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Clinical Aspects of the Metabolic Response to Trauma

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MAN may receive so many different kinds of injury that any account of the nature and variation of his metabolic response to each must, if it is to maintain reasonable brevity, be somewhat selective. Accordingly, this review will be written mainly from a clinical standpoint and will be concerned chiefly with hemorrhage, thermal burns, soft tissue injuries, head injuries, bone fractures, and surgical trauma. It will endeavor to present the numerous metabolic changes which follow trauma in such a way that they may be useful, first, in assessing an individual patient's metabolic state, and, second, in forming a logical basis for his fluid therapy. The extensive investigations of laboratory animals, sometimes following types of trauma rarely met with in man, will be considered only where they are relevant to this main theme. Within this limited field there are two major topics, blood transfusion after hemorrhage, and postoperative fluid replacement, in which further selection of material has been necessary.

METABOLIC CHANGES RESULTING FROM TRAUMA

Changes of Body Fluid Distribution

The movement of water and electrolytes between the body compartments after injury has been studied mainly in animals (for references, see reviews 1–4), but direct information is available in man after surgical operations[5] and thermal burns.[6] Whatever the type of trauma, the primary change is loss of fluid from the intravascular compartment. This occurs at the site of injury and is of two sorts, (a) loss to the exterior when there is an open wound of the skin or gastrointestinal tract, and (b) loss by exudation into damaged tissues whether the skin is intact or not. Whole blood, a protein-rich exudate, or a mixture of both is lost, depending on the extent to which blood vessels are either ruptured or made more permeable. Studies with radioactive plasma protein[7] indicate that there is no exudation of protein in the undamaged tissues. The factors promoting increased capillary permeability at the site of injury are little understood, but the exudative loss so produced may be considerable, and its magnitude may often be underestimated clinically. Courtice[8] has shown, for example, that thermal burning of both hind legs of the rabbit below the knee may lead to an accumulation of fluid greater than the original plasma volume. Such exudative losses at the site of injury appear to be obligatory. There is some evidence that cooling or compression of the part with bandages will greatly minimize fluid extravasation,[4] but this is disputed.[6] Fluid lost into damaged tissues begins to be reabsorbed after about 48 hours if the patient survives.

Fluid begins to move almost at once after injury from the extracellular spaces of undamaged tissues into the intravascular com-

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partment, in order to compensate for local fluid loss. The extent to which compensating fluid is also derived from intracellular spaces has not been fully investigated and possibly varies with the type of trauma, the state of hydration of the body, and the rate of fluid loss, but it would seem, after hemorrhage and burns[9,10] at any rate, that the transfer of water from cells occurs relatively slowly, if at all. In the initial stages, therefore, most of the compensating fluid is derived from the extracellular compartment, bringing with it sodium and chloride ions but little protein. It has been observed, however, in battle casualties with limb injuries,[11] that significant amounts of protein are added to the blood after about six hours. Whether this change portrays the arrival of intracellular water or merely reflects the relatively slow diffusion of protein from reserves is obscure. The prevention of hypotension and shock depends partly at least upon the extent to which these fluid shifts are swift enough and large enough to keep pace with fluid loss.

Changes of body fluid distribution differ somewhat from this general pattern after head injury. Although exudation of fluid may occur at the extracranial site of injury, its accumulation at the intracranial site is limited by the relative rigidity of the bones of the skull. Despite severe contusive injury and a considerable rise of intracranial pressure, the actual loss of fluid from the intravascular compartment may be small and easily made good from undamaged parts of the body. Hypotension rarely develops, therefore, after head injury in the absence of damage to other parts of the body, or of direct injury to the brain-stem.

Increased Catabolism

Immediately after injury there may be a phase in which body metabolism is depressed, with subnormal temperature,[12] but if the patient survives, this gives way to a phase of excessive protein breakdown with increased oxygen uptake and often a slightly raised body temperature. Cuthbertson[12] has shown, following fractures and other bone injuries, that there is a negative balance of nitrogen, potassium, sulphur, and phosphate which reaches a maximum between the fourth and eighth days and thereafter returns to normal. The more extensive the injury, the greater the increased catabolism. Similar changes have been found after surgical trauma and burns.[5,6,13,14] Careful studies[15] have indicated that these losses are greater than may be accounted for by fever, infection, or disuse atrophy, and that they are, like the fluid loss, obligatory. High caloric, low protein diets reduce the negative balances but do not prevent them. Several workers[16,17,18] have succeeded in maintaining positive nitrogen balances at all stages after injury by feeding diets with high caloric and protein contents, but the amounts required are excessive. Others, however, have failed.[19] Evidence indicates that carbohydrate and fat may also be broken down more rapidly.[20-24] Moore *et al.*[24] have found that up to 600 gm of fat per day may be utilized in surgical patients following operation.

The mechanism of this increased catabolism after trauma is unknown. It depends to some extent on adrenal cortical activity (q.v.) and may also be related to the presence of increased amounts of circulating peptidase in the blood.[25,26] Peters[27] suggests that there is an abeyance of protein synthesis after injury during which amino acids are not being used for protein anabolism; Cuthbertson[28] suggests that the increased breakdown of protein serves to provide energy or amino acids or both for the healing process, and that this is a "primitive response independent of food, for a wounded animal is necessarily reduced in its capacity to feed itself."

Disturbances of Renal Function

(a) *Without Apparent Tissue Damage.* Renal function is usually disturbed after trauma, although sometimes after head injury there may be no apparent dysfunction.[29,30] The earliest and most usual change is oliguria, which has long been considered to arise from reduction of renal blood flow because of hypotension or reflex renal vasoconstriction, or of both. However, even after mild trauma, or when a significant degree of hypotension is prevented by treatment, there

may be a transient period of "primary water retention"[31] in which the urinary output is always much less than the intake, although with intakes of up to 4 liters of fluid the urinary output may be as high as 1.5 liters in the first 24 hours after injury.[31,32] Evidence has been adduced[31,33] that such retention, after surgical trauma at least, is brought about by excessive secretion of antidiuretic hormone from the posterior pituitary. Unless hypotension persists (q.v.), the urine is usually well-concentrated[32] with a urea concentration exceeding 2 gm per 100 ml.[34] This phase of primary water retention may persist for a varying period of one to five days, depending upon the type of injury and its severity, even though the blood pressure may return to normal much earlier.

The kidneys also retain sodium and chloride ions after injury. Retention usually begins on the first or second day and lasts for five days or more.[5,32,35] Le Quesne and Lewis[31] have divided this period into early and late stages after surgical operations. Retention occurs despite abundant provision of sodium. Evidence has been adduced that sodium retention is accompanied by and perhaps caused by the liberation of excessive amounts of adrenal cortical hormones.[5,36] Ingle,[37] however, finds that sodium retention occurs after trauma in adrenalectomized animals that are maintained on a constant intake of adrenal cortical hormones. During the period of sodium retention, serum sodium levels are usually normal or low. There is no absolute barrier to the excretion of sodium and chloride, and, although some is always retained, the more sodium given the more is excreted.

Water and sodium retention may be looked upon from the renal point of view as physiological adaptations to the local fluid loss of trauma which are going to occur whether or not the loss is replaced therapeutically. There is little doubt, however, that renal function may be pathologically, although transiently, disturbed after injury, even in the absence of hypotension, renal ischemia, or shock. Thus, proteinuria and cylindruria may occur during the first 24 hours of injury, diminishing gradually over a period of two to six days;[32,34] and transient glycosuria without hyperglycemia has been found after head injury.[34] Significant reduction of glomerular filtration rate and PAH clearance may also occur after wounding without clinical evidence of shock.[38] A second type of sodium retention has been described in which the kidneys set up a more or less absolute barrier to sodium and chloride excretion, while maintaining adequate outputs of water, urea, and potassium. Consequently there is hypernatremia, hyperchloremia, and sometimes edema. This biochemical syndrome has been described after head injury,[34,39,40,41] hemorrhage,[42,43] and operation.[44] Its mechanism is obscure, but there seems to be general agreement that adrenal cortical stimulation is not a main factor. Hemodynamic factors, cerebral damage, and diabetes insipidus have been variously incriminated. The reverse picture, of excessive renal excretion of sodium and chloride despite low serum levels, may occur during the second week after head injury.[34] The patients become dehydrated but have no demonstrable adrenal deficiency either clinically or post mortem and do not respond to treatment with adrenal cortical hormones. A similar picture of "continued unregulated renal sodium loss" has been described following surgical operation as part of the "hypoadrenal response."[5] Renal uremia has also been described following head injury.[34] Patients may develop a rapidly rising blood urea with failure to concentrate urea in the urine above 1.5 gm per 100 ml. Proteinuria, oliguria, and hypotension may be absent, and the kidneys may appear normal at autopsy, so that this disturbance differs somewhat from the acute renal failure about to be described.

(b) *With Tissue Damage.* When trauma is followed by a period of renal ischemia due to persisting profound hypotension or to renal vasoconstriction, there may occur, in addition to and superimposed upon the renal disturbances already described, acute renal failure associated with definitive histological lesions. Many names have been given to this defect: shock-kidney, crush syndrome, acute tubular necrosis, lower nephron nephrosis, and tubulo-

rhexis. It has been described following burns,[29,45,46] hemorrhage,[29,47] surgical operations,[46] and crushing of the limbs.[48] The patient passes no urine or only very little. It usually contains protein and casts and may contain myohemoglobin after crushing injuries. The specific gravity is characteristically low[49] and the urinary urea concentration is usually less than 1.5 gm per 100 ml. The essential factor common to all the conditions in which acute renal failure has been described would seem to be renal ischemia, usually following profound, persistent hypotension and exacerbated by other factors such as casts, myohemoglobinuria, and renal afferent arteriolar constriction. Anatomical lesions develop about 30 hours after the onset of renal failure[49] and are confined to the tubule. They have been called adhesive[50] or nephrotoxic[46] where there is no break in continuity of the tubule, and disruptive[50] or tubulorhexic[46] when there is. Nephrons with the latter type of lesion heal with obliterative fibrosis and do not recover their excretory function. Patients in whom they occur may survive the initial trauma but die some days later in renal failure. In those patients who recover it would seem that none or only a minority of nephrons have reached the disruptive or tubulorhexic stage.

Liver Function and Intermediary Metabolism

Studies of liver function after trauma have been primarily concerned with disturbances occurring after profound "shock," when the portal blood flow may be greatly reduced and its oxygen saturation fall from the normal 15 vol. per 100 ml to 5.[51] Sonsiderable hypoxic damage may therefore ensue if reduced flow persists for long, and these two factors may together be responsible for the disturbed intermediate metabolism which has been observed in shock.[23] Urea production, for example, may diminish and amino acids increase in blood and liver. Lactate may also accumulate and high-energy phosphate compounds be depleted. During recovery from shock, some of the enzyme systems whose activity has been merely depressed recover rapidly, but others which have suffered damage, notably those concerned in the manufacture of fibrinogen and prothrombin, recover more slowly (J. Fine[23]). During hypoxia of the liver there is also evidence that the irreversible stage of shock is promoted by failure to inactivate in the liver a vasodepressor substance (VDM), which may be identical with ferritin.[52] Apart from these changes, trauma not involving shock or hypotension may disturb liver function transiently. Cole *et al.*,[53] for example, find impairment of a number of liver functions following surgical operation. Whether the liver plays a fundamental role in the genesis of irreversible shock or not, it is apparent that following trauma its ability to carry out its normal metabolic transformations may be curtailed, and this must be remembered when nutrition is being considered.

Endocrine Function

Much experimental work has been devoted to studying the function of the pituitary and adrenal glands after trauma, but their precise metabolic role is still obscure. There is evidence that the transient rise of blood sugar which may occur immediately after injury results from liberation of adrenal medullary hormones,[23] although other workers have denied this.[54] The negative balances of nitrogen, potassium, and phosphate, and the retention of sodium which follows trauma are thought to depend at least partly on the adrenal cortex, for they are absent in the adrenalectomized animal, and the administration of corticotropin (ACTH) or cortisone to normal animals will promote similar changes of balance. It has been shown, however, that such changes do not result from an increased liberation of corticoid hormones after trauma, for they occur as readily in the adrenalectomized animal maintained on a constant dose of hormone.[37] Furthermore, the amounts of hormone necessary to promote comparable changes of balance in normal animals appear to be pharmacologic rather than physiologic. Nevertheless, it seems well-established from studies of ketosteroid excretion that increased amounts of adrenal cortical hormones are produced after trauma, whatever their function or relationship to metabolic changes.

The posterior lobe of the pituitary gland

may be damaged by head injury or neurosurgical operation, and diabetes insipidus sometimes results. This is easily diagnosed if the patient is conscious, but if unconscious and incontinent of urine, the diagnosis may be overlooked and dehydration may follow.[41]

Gastrointestinal Function

Despite the importance of the gastrointestinal tract in fluid, electrolyte, and nutritive replenishment after trauma, little is known of the extent to which its digestive and absorptive functions may be impaired. After most severe injuries there may be a general tendency to vomit, particularly if there has been a recent bulky meal, and secretions may "pool" in the stomach rather than pass on into the intestine. These effects are, however, often transitory and, after head injury at least,[34] water, electrolytes, milk, and glucose are readily assimilated from the gut 12 hours later. Cuthbertson[15] has noted following bone fractures that absorption of digestion products from the gut cannot be appreciably affected, as in only one case did the fecal nitrogen excretion exceed an average of 2 gm a day. The extent to which this remains true in more severe injuries involving hypotension and shock is, however, unknown, although there is evidence that absorption of glucose and saline may be impaired.[55] Direct damage to the gut, either by accident or after abdominal surgery, may of course interfere considerably with gut function, particularly if paralytic ileus should supervene, and acute ulceration of the upper intestine following burns and neurosurgical procedures has been known for many years.

Post-Traumatic Anemia

Anemia of varying degree is often found after trauma and during the convalescent period, and has been accepted as the logical consequence of hemorrhage at and after the time of injury. There is usually a rapid fall of hemoglobin concentration during the first two to five days after injury, and the lowest levels are reached between the third and fourteenth days, followed by a gradual rise. After head injury, however, the hematocrit in unconscious patients may remain below 40 per cent for from three to eight weeks, despite an adequate intake of hemopoietic factors and a high protein diet.[30] Post-traumatic anemia may also develop even after large and apparently adequate transfusions of blood,[11,56,57] and although blood volume estimations have shown that this anemia is due in part to an increased plasma volume,[11] there seems also to be a continued loss of red cells from the circulation even in the absence of bleeding or infection. Clarke[57] concludes that after wound trauma more blood disappears than has been lost to the exterior or shed into tissues, and suggests that red cells are used up in the advancing capillary buds of granulation tissue, presumably for anabolic purposes. Plasma protein concentration may fall initially in a similar fashion to hemoglobin, but may return to normal more swiftly.

Variations in the Metabolic Response

In general, the more severe the trauma, the greater the metabolic responses which have been described. Undoubtedly, however, some patients may give an excessive response after only a moderate degree of trauma.[5] Of more importance, perhaps, is the nature of the response to trauma in the previously ill or debilitated subject. All balance changes are smaller than might be expected and particularly is this so of protein breakdown. The body proteins of a malnourished patient are less vulnerable after trauma than those of a normal subject, and it is easier to promote a positive nitrogen balance in such a patient. Despite this adjustment of metabolic response, such patients fare worse than normal subjects.[5,30] A patient previously dehydrated, e.g. from intestinal obstruction, is also at a disadvantage, for the mechanisms of fluid adjustment during subsequent trauma are equally at play, as in a normal subject, but pre-existing dehydration makes effective replacement of intravascular loss more difficult, and blood pressure falls more readily.

A hypoadrenal type of response has also been described after surgical trauma,[5] characterized by "continued unregulated renal sodium loss and intractable hypotension with

a favourable response to adrenal cortical hormones." It occurs in patients with Addison's disease and panhypopituitarism, but more often when there is only functional adrenal sufficiency which improves with recovery from trauma.

Metabolic Effects Arising Secondarily

In addition to the general metabolic effects which have just been considered, many of the sequelae of trauma may secondarily affect metabolism.

Injury to Specific Organs. Direct damage to the gut, liver, or renal tract may produce specific effects which are superimposed upon the general metabolic response, for example, hematuria, anuria, peritonitis, paralytic ileus. When the brain stem is damaged after head injury or neurosurgical operation, hyperpyrexia and hyperventilation may result, and the latter is sometimes sufficient to produce a marked respiratory alkalosis.[34]

Infection. If a traumatized site becomes infected, or more commonly if hypostatic chest infection develops, a number of metabolic effects follow. Fever results in excessive water loss from the lungs and skin and increased sodium loss by sweating. The maintenance of a high body temperature causes increased energy production, which, if not obtained from food sources, must be met from body tissues, with consequent exaggeration of negative nitrogen balance, production of greater loads of urea and potassium for excretion, and increased production of ketone bodies. Fluid may also be lost at the site of infection, particularly if there is peritonitis.

Food and Fluid Deprivation. Patients may take little food or fluid for some hours after trauma, particularly if unconscious, if there is a fracture of the jaw, or if they are awaiting operation. The reduced fluid intake will, if not replaced, tend to produce water deprivation, and the reduced food intake to increase further the catabolic breakdown of body tissue.

Surgical Operation. Early operative treatment is often essential after any form of trauma, but must be regarded from the metabolic point of view as an additional injury for the body to withstand. All operations involve some loss of blood and tissue fluid, which further strains the limited fluid resources of the body.

Continuing Fluid Loss. Fluid may continue to be lost from the body after trauma by a number of routes, such as fistulae following surgical operation, exudation from burns, loss of cerebro-spinal fluid as rhinorrhea. All such losses must be met from the extracellular fluid compartment of the body and may result in fluid, electrolyte, and protein loss, unless replaced.

Assessment of Metabolic State After Trauma

It is apparent from the preceding section that the metabolic state of an individual patient at any one time after trauma will be the resultant of many changes, and the clinical problem is to piece together from the static picture obtained at consultation the whole dynamic process of what has happened, what is happening, and what is likely to happen, and upon this to base treatment. With a knowledge of the metabolic changes of trauma as a background, three sets of information are available to solve this problem. These are the clinical history, clinical examination, and examination of the blood and urine. It should be emphasized that the metabolic state may have to be assessed relatively quickly, so that some determinations, such as blood volume and thiocyanate space, which give precise information in the laboratory are only available in retrospect in the ward. Indirect methods of estimation may therefore need to be adopted. Furthermore, the clinical course following different types of trauma varies widely, and much of what follows will necessarily apply to only one or a few forms.

Clinical History

No aspect of the clinical history should be ignored, but certain items are of special importance, and particularly so the fluid balance chart. This should record all the fluid that has entered the patient and all that has left by way of urine, vomitus, or other loss. If clearly tabulated and accurately kept, the data

on the fluid chart provide a most reliable contribution to precise metabolic diagnosis and treatment. Conversely, if kept inaccurately, the chart may do more harm than good. It is also important to keep exact records of body temperature and blood pressure. From the former may be obtained knowledge of the degree of insensible water loss, and the latter may perhaps provide an explanation of uremia and oliguria occurring four days after a hypotensive episode.

The problems associated with the clinical history are, therefore, mainly those of good organization and careful recording, and if these are adequate it should be relatively easy to obtain a first quantitative estimate of fluid retention or dehydration, and particularly of which fluids, water, blood, plasma or extracellular fluid, are lacking or have been given in excess.

Clinical Examination

A second assessment of the extent and nature of fluid imbalance may be obtained from general clinical examination and from examination of the wound site. Several schemes have been proposed to evaluate clinical data in quantitative terms. Marriott,[58] studying dehydrated patients, has been able to convert thirst, blood pressure, and other signs into quantitative deficits of water and sodium, but unfortunately pure deficits of these substances are rarely met with in dehydration after trauma. Cope and Moore,[6] studying burned patients, calculate that for each 1 per cent of the body surface burned, 75 ml of plasma and 75 ml of non-colloid-containing isotonic electrolyte fluid are lost locally during the first 24 hours. Grant and Reeve[11] have evaluated blood loss after war wounding in terms of blood pressure and wound size by direct calibration against blood volume determinations. Wound size was estimated in units of the volume of the patient's hand, so that small wounds with tissue damage of less than one hand usually caused a loss of 10 per cent of the blood volume, and very large wounds, of five or more hands, of as much as 50 per cent. This method proved to be of great value in limb and skin wounds, but less so in abdominal injuries, because of the difficulty of assessing wound size. A systolic blood pressure of over 140 mm Hg usually indicated at least a blood volume of 80 per cent of normal, a pressure of 100–140 mm a blood volume of 70 to 80 per cent of normal, and a pressure below 100 mm a blood volume below 70 per cent of normal.

Even if no quantitative assessment can be obtained, examination of skin turgor, tongue, eyeball tension, sacrum, legs, neck veins, lung bases, and blood pressure may give qualitative information about the degree of over- or underhydration, and examination of the cardiovascular system and abdomen should precede any decision about the use of intravenous or oral fluid replacement. The urinary output should always be ascertained, by catheterization if necessary, but attempts to use it as a guide to fluid requirements are dangerous in view of the many factors which may promote oliguria and water retention after trauma. The promotion of a normal or high urine flow after trauma usually requires a high intake of fluids and causes a high positive fluid balance.

Examination of the Blood and Urine

Biochemical composition of the blood and urine may alter little within the first few hours of injury, despite severe hemorrhage or exudation, and the patient's metabolic state must at this time be assessed mainly on clinical grounds. Analyses of blood and urine become important, however, if there is unconsciousness, inability to swallow, excessive postoperative fluid loss, or depression of renal function; from them a third independent assessment of the metabolic state can be made. The findings must always be interpreted in relation to the patient's clinical signs. A low serum sodium or chloride concentration has, for example, a very different meaning in an edematous patient than in one obviously dehydrated. The various interpretations of such biochemical data are considered below.

Hematocrit, Hemoglobin, and Plasma Proteins. When trauma produces little hemorrhage but much tissue damage with local fluid loss, red cells are concentrated in the intravascular compartment and the hematocrit rises. This occurs principally after burns and

sometimes after operation when there is dehydration. Under these circumstances, the high hematocrit is a measure of the extent to which local fluid loss from the vascular system exceeds the entry of fluid from extravascular sources. Serial hematocrit readings may therefore help to follow the course of fluid loss and rehydration, always provided there is no hidden hemorrhage. Some schemes of fluid replacement following burns aim to keep the hematocrit constant at a normal level. It would seem, however, that such a method underestimates fluid requirements, as it takes no account of the movement of fluid from tissue spaces and cells into the vascular system. A high hematocrit is undoubtedly a valuable sign of blood volume depletion, but a normal or low value may occur when there is considerable fluid depletion in the other body compartments. It should also be remembered that the hematocrit tends anyway to fall after trauma, possibly because hemoglobin is used anabolically. Estimations of hemoglobin and plasma protein concentrations yield similar information to the hematocrit, but plasma protein may be used up or replaced from reserves and its concentration therefore varies independently of the blood volume.

Blood and Urinary Urea. Many factors combine to raise the blood urea concentration after trauma, the chief of which are the excessive protein catabolism of injury or infection, lack of energy from exogenous sources, and depression of renal function. The main interest centering around a raised blood urea concentration is to know whether it indicates renal damage or not, and in this respect the urinary urea concentration is particularly helpful. If the concentration is high, over 2.0 gm per 100 ml, the factors promoting a high blood urea are principally extrarenal. If less than 2 gm per 100 ml, a pathologic disturbance of renal function is indicated, and the patient must have had renal disease preceding the injury or be developing acute renal failure or the renal uremia of head injury. A history of previous renal disease, polyuria, and nocturia should then be sought, and the fundal vessels should be examined and evidence of hypertension looked for, in order to differentiate between these conditions. If the first specimen of urine passed after trauma happened to be concentrated and have a high urinary urea concentration, then a low urinary urea concentration in the presence of a high blood urea might now indicate the development of acute renal failure. When a patient is severely injured and likely to suffer from the effects of trauma for some time, it is a good plan to obtain for analysis the urine that was in the bladder at the time of injury. No significance can of course be attached to such a urine if it happened to be dilute and have a low urinary urea concentration.

Serum and Urinary Sodium and Chloride. The dangers of interpreting serum sodium and chloride concentrations without reference to the clinical state of the patient have already been emphasized, and it is well known that a moderate deficit or excess of sodium may sometimes be present with normal serum sodium and chloride levels.[58]

When, after trauma, the serum sodium and chloride concentrations are found to be low, there may be several explanations. If the patient is dehydrated, the most usual cause is sodium deficiency due to loss of extracellular fluid, and the urinary sodium and chloride concentrations are usually also low, less than 17 mEq/lit (1 gm NaCl/lit), but may be higher if intravenous infusion of saline fluids is taking place.[44] Dehydration with low serum sodium and chloride concentrations may also be produced by excessive urinary loss of these ions in Addison's disease, panhypopituitarism, the hypo-adrenal response[5] and in some elderly patients after head injury.[34] If the patient is normally or over-hydrated and the serum sodium and chloride concentrations are low, there is either congestive cardiac failure or water intoxication. The latter condition occurs when there is an excessive intake of low sodium-containing fluids by vein or, more rarely, of water by mouth or rectum.[59] It arises particularly when there is oliguria of either renal or extrarenal origin, so that renal damage, hypotension, and obstruction to urinary outflow should always be sought when water intoxication occurs.

A raised serum sodium and chloride concen-

tration in a dehydrated patient indicates water deficiency and is found in patients who cannot swallow because of weakness, coma, or esophageal obstruction, and also after head injury or neurosurgical operation when diabetes insipidus supervenes in an unconscious patient.[30,41] In simple water deprivation the urinary sodium and chloride concentrations are usually high (above 17 mEq/lit) and so is the specific gravity of the urine, whereas in diabetes insipidus the concentrations of sodium and chloride and the specific gravity are low. When high serum sodium and chloride concentrations with low urinary concentrations are found in normally or over-hydrated patients, there is failure of the kidneys to excrete these ions because of renal damage or the type of sodium and chloride retention referred to earlier (which has been called the hyperchloremic-hypochloruric syndrome). If urinary concentrations are high and the patient normally or over-hydrated, raised sodium and chloride concentrations indicate that previous fluid and sodium therapy has been carried out with too great a quantity of isotonic electrolyte fluid.

Plasma chloride concentrations may sometimes be raised but the serum sodium level remain normal. This happens in respiratory alkalosis following brain-stem damage, where the chloride rise is compensatory for the low plasma bicarbonate level produced by hyperventilation. It may also occur during intravenous infusion of isotonic sodium chloride, which has a sodium concentration similar to that of serum (150 mEq/lit) but a much higher chloride concentration (150 as against 100 mEq/lit). It may also be the first indication of hypernatremia, for chloride enters cells less readily than sodium, so that its extracellular concentration increases more quickly than that of sodium when both are tending to rise.

Emphasis is sometimes placed upon the usefulness of urinary chloride concentrations in diagnosing sodium deficiency.[58,59] There is no doubt that in experimental sodium deficiency the urinary chloride concentration may fall before the serum sodium concentration and thus give an early indication of sodium lack,[60] but this need not hold true after trauma. Trauma is itself followed by a low sodium and chloride output in the urine, and several situations have already been discussed in which high serum sodium levels are accompanied by low chloride levels and vice versa. The interpretation of such a test depends, moreover, on the concentration of urinary chloride which is considered low, and values of up to 3 gm NaCl/lit (50 mEq/lit) have been suggested.[58,59] The author's experience with patients after head injury or operation would, however, support the view that only concentrations below 17 mEq/lit can be considered low, and that the use of higher figures as a basis for therapy would lead to the over-hydration of many patients. Several workers[35,61,62] have arrived at similar conclusions concerning the diagnostic value of urinary chloride determinations.

Serum Potassium. Excess or deficiency of potassium is uncommon after trauma unless there is oliguria or excessive loss of gastrointestinal secretions. In the former instance, the serum concentration of potassium rises because increased amounts of it are released by the excessive protein catabolism of trauma and are retained. In the latter instance it falls because gastrointestinal secretions may contain up to four times as much potassium ion as the serum from which they are derived. Losses of potassium from the serum in this way can to some extent be made good by liberation of potassium from the cells, and the author has found in postoperative cases that daily losses of up to 600 ml of gastrointestinal secretions do not usually cause lowered serum potassium levels, but that if losses exceeding this amount occur for more than 48 hours, a low serum potassium level may follow. A careful watch should therefore be kept upon serum potassium concentrations when the urinary output is low or loss of gastrointestinal secretions has persisted for 48 hours.

Fluid Therapy and Nutrition After Trauma

The aims of fluid therapy after injury are to prevent the onset of adverse metabolic changes, to treat those which do arise, and to promote healing and regeneration of damaged

tissue by maintaining the internal environment as nearly normal as possible and by supplying the necessary food materials in an assimilable form. There are three stages in the achievement of these aims. The first, arising during the first 24 hours after injury, is the replacement of acute fluid loss. The second, usually occupying two to five days, is a stage of adjustment, in which fluid, electrolyte, and nutritional requirements are adjusted to minimize any adverse effects which the metabolic response to trauma may bring forth. The third is the stage of repair, in which therapy assists regeneration of damaged tissue and replacement of the general losses of the preceding days.

A. REPLACEMENT OF ACUTE FLUID LOSS

Blood volume depletion may not only cause early death but also play a prominent part in the development of irreversible shock and acute renal failure, so that acute losses of fluid should be replaced early and in amounts adequate to maintain the blood volume above 70 per cent of normal.[11] The precise volumes required are assessed by the clinical methods of the last section. Following hemorrhage, blood should be given, and following burns, a colloid fluid such as plasma, human albumin solution, dextran, oxypolygelatin, or polyvinylpyrrolidone should be given. Infusions are usually intravenous, but in patients with severe hemorrhage and hypotension, blood may be replaced intra-arterially,[63] although recent work suggests that the occasions on which such a procedure confers any real advantage are few.[64,65]

Choice of Colloid Fluid

The choice of a suitable colloid fluid for infusion has been the subject of much recent research which cannot be fully documented here. Physiologically, the correct replacement for exudations of protein-containing fluid is plasma or human albumin solution (which is not now available in Great Britain), together with an appropriate quantity of electrolyte solution. Three substitutes, dextran, oxypolygelatin, and polyvinylpyrrolidone, are available and it has been claimed for the first of these[66] that when its molecular size is carefully chosen it is a better plasma volume expander than plasma, although comparative data are not given. Dextran has also been found clinically satisfactory in treating battle casualties in Korea,[67] and a warning is given that it is sometimes so effective in abolishing shock that low hemoglobin levels may be overlooked and anoxia develop. A comparative clinical trial[68] of dextran, gelatin, serum albumin, and plasma on orthopedic patients "in good condition clinically," in which effectiveness was judged by the observed expansion of blood volume at different times after the infusion of osmotically equivalent quantities, has led to the conclusion that plasma has the least effect of all as a plasma volume expander. Work on animals[69] confirms that dextran gives a greater and more prolonged expansion of blood volume than plasma or oxypolygelatin. When, however, the various colloid solutions are judged by their effect on the survival of animals after standardized hemorrhage[70] or burns,[71] it would appear that dextran and plasma are equally effective and a whole blood-plasma mixture more so.

Another method of assessment, and one that would seem to have important clinical applications, is to determine the fatal rebleeding volume in animals after replacing a standard hemorrhage with various colloid solutions.[70] It was found that this volume is significantly higher in animals treated with plasma than in those treated with dextran or oxypolygelatin. The relative effectiveness of plasma and its substitutes does, therefore, seem to depend somewhat upon the method of assessment, but there is little doubt that all are more effective than saline alone.

Certain other factors also govern the choice of colloid fluid. Hepatitis may follow plasma infusion but has become rare with modern methods of plasma preparation. The substitutes, particularly dextran, are also not free from side-effects. Allergic reactions,[72] intravascular aggregation of red cells,[70] and depressed renal function[73] have been described. The question also arises as to how much of the substitute may be given. After burn injuries, for example, several liters of colloid

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fluid are often required, and while such a quantity of plasma may be given readily, some compunction might be felt over the infusion of an equal volume of a substitute. A further question which has received little consideration is the possibility of plethora when reabsorption of fluid from tissues begins about 48 hours after injury. If a large volume of plasma has been given, its protein components may always find their way into reserves or be catabolized, but the substitute substances are less readily disposable. The author feels that there is as yet no good evidence that the substitutes confer any significant advantage over plasma, and that infusions of them should not exceed 1500 ml in volume.

B. MANAGEMENT OF ADVERSE METABOLIC CHANGES

Prevention

When, where necessary, acute losses of fluid have been replaced, the further nutrition and fluid therapy of the patient must be considered. If he is able to swallow, and the necessary surgical measures have been completed, it is usually sufficient to give a light diet of adequate caloric content and allow fluids as desired, provided that a check is kept on their volume and on the urinary output. If, however, the patient is unconscious or very weak, or if the gastrointestinal tract must be rested because of injury or operation, fluids must be given by intragastric tube or intravenously, and it is in these circumstances that over- or under-administration may arise. At this stage after injury there is likely to be some limitation of urinary output of water, sodium, and urea, and therapy must be adequate without causing undue retention of these substances.[87]

Water and Sodium Intake. Water intake should aim to replace measured urinary and other losses together with approximately 1000 ml to allow for insensible loss. If there is fever, this latter figure may be increased by about 200 ml for each degree above 100° F.[30] Similarly, sodium intake should aim to replace losses of isotonic fluids, if any, together with a supplement of 0.5 to 2.0 gm daily to cover small losses such as those from the skin surface and sputum. There is usually no need to replace urinary losses unless they are excessive.[5] In this way, water and sodium deprivation may be prevented without causing an excess of either, and it should be remembered that from 48 hours onwards isotonic fluid is likely to become available to the body compartments by reabsorption from damaged areas and may need to be excreted.

Caloric and Protein Intake. Every effort should be made to provide a high caloric intake—otherwise, body tissue is catabolized to provide energy; body reserves are unnecessarily depleted; excessive amounts of urea and ketonic bodies are formed; and the excretory work of the kidneys is increased. Although high calorie, high protein diets have been devised which will allow a positive nitrogen balance to be maintained, it is the view of most workers that high protein intakes at this stage after trauma are wasted.[5,27,28,74] From another aspect, that of maintaining the constancy of the internal environment, the amount of protein which should be allowed depends very much on the blood urea concentration and the urinary output. If there is anuria, none should be given. If, as is usually the case after head injury, the daily urinary output exceeds 500 ml, a moderate amount may be advised. Thus, in 50 cases of head injury treated with a diet containing 59 gm of milk protein,[34] the blood urea concentration only exceeded 100 mg per 100 ml in four. When the blood urea is above 100 mg per 100 ml, protein intake should be decreased and replaced by an equivalent amount of carbohydrate, for, although urea may not in itself be harmful, there may be retention of other materials such as sulphate and phosphate, and a high urea concentration is in any event a poor starting point should further hemorrhage or fluid loss occur or operative treatment be needed. High calorie, low protein diets in which the amounts of water and sodium are carefully regulated should, therefore, be given at this stage after injury.

Intragastric Tube-Feeding

A milk-glucose regime which goes some way to meet these requirements when nutrition is

to be maintained solely by pernasal intragastric tube has been described[34] and is suitable for use in unconscious patients after head injury, or neurosurgical operation. The total daily intake of fluid varies from 4 to 6 pints (2250 to 3400 ml), that of protein (milk) is 50 gm, and of sodium 0.85 gm (approximately 2 gm NaCl). The caloric value of 2250 cal daily is provided by milk and 400 gm of glucose. The latter is usually well tolerated, without causing diarrhea, and the whole is readily assimilable. The amount of sodium may be increased as soon as it is established that the kidneys are able to excrete this ion and that hypernatremia is thus unlikely to occur. When the blood urea concentration returns to normal levels, a higher protein diet is begun.

Intravenous Therapy

When fluids must be administered mainly by vein there is usually no difficulty about replacing water and electrolyte losses unless these are excessively large. It is sometimes difficult, however, to combine with these substances a high caloric intake. Isotonic glucose solutions (5%) supply only 200 cal per lit, and hypertonic solutions promote venous thrombosis, requiring a different site of administration every 24 hours or so. Attempts have recently been made to overcome these difficulties by infusion of fructose, alcohol, or fat emulsions.

Fructose may be given alone or with an equal quantity of glucose as inverted sugar. If given in 10% or 15% solution fairly rapidly, e.g. 1 liter in 90 minutes, fructose has been found to be more rapidly assimilated than is glucose, and less of it lost in the urine.[75,76] There is, however, contradictory evidence[77] indicating that 10% fructose given in amounts of up to 3 liters for several days is not retained as well as 10% glucose and is associated with a definite increase in electrolyte excretion when compared with the latter. Venous thrombosis does not seem to occur when these short infusions are given.

Alcohol has been infused in 7–10% concentration at a rate of 40–80 drops per minute and amounts of $1^1/_2$–$2^1/_2$ liters given in 24 hours.[78,79] The site of administration is changed daily. Since 1 gm of alcohol is equivalent to approximately 7 cal, as much as 1750 cal may be supplied each day if all the alcohol is catabolized. Blood alcohol levels reach 30 to 100 mg per 100 ml, and inebriation occurs if the latter value is exceeded. Alcohol is contraindicated in shock because of its vasodilator effect. Rob[80] recommends an infusion mixture of 5% glucose, 5% fructose, and 6% alcohol, containing 820 cal per lit. Fat emulsions (15%) have also been used intravenously in amounts up to 1 liter daily, thus providing 1350 cal[81] if fully utilized.

Although, for the reasons already given, the provision of a high caloric intake is desirable, it must be remembered that the primary function of intravenous therapy must always be to maintain fluid and electrolyte balance. If while doing this an adequate calorie diet can be maintained by infusion of some of the substances mentioned above, so much the better, as long as an adequate number of veins are left undamaged to continue water and sodium replacement.

Correction of Metabolic Disorders

Although replacement of acute fluid losses and careful adjustment of water, sodium, and caloric intake should prevent adverse metabolic changes, the latter may occur and require special consideration.

Disorders of Water and Sodium Balance. Water deprivation, water intoxication, sodium depletion, and sodium intoxication may be recognized by the methods described in the preceding section and the cause of each similarly ascertained. Water deprivation should be treated by administration of water by mouth or 5% glucose solution intravenously, and sodium chloride depletion by isotonic sodium chloride orally or by vein, until the patient is normally hydrated with normal serum sodium and chloride concentrations. When water deprivation is caused by diabetes insipidus, or sodium deprivation by the hypoadrenal response, post-pituitary and adrenocortical hormones, respectively, should also be given. Water intoxication should be treated by limiting water intake and infusing hypertonic solutions of sodium chloride.[59,82]

Hypernatremia and hyperchloremia caused by inability to excrete sodium and chloride ions usually respond to a low sodium and high water intake.[34]

Potassium Imbalance. When gastrointestinal secretions are being lost and replaced by sodium-containing fluids, serum potassium depletion may occur and may be treated by adding potassium chloride to the infused fluids.[5,69,83] Potassium chloride may also be given by mouth, even if aspiration from the stomach or intestine has to be carried out hourly,[30] although this is not widely known. After one aspiration, potassium chloride solution is introduced into the gut and left until the next. Its concentration in the gut is so high compared with that in serum that, although fluid diffuses into and accumulates in the gut, potassium will diffuse out into the extracellular fluid in amounts sufficient to maintain normal levels. If too much is given, high serum levels may even be obtained. The quantities of KCl required when aspiration is carried out hourly or two-hourly have been found to vary with the amount of fluid aspirated according to Table I.

TABLE I

Requirements for Potassium Replacement

Daily volume of aspiration		KCl required per day
ml	*oz*	*gm*
0–600	0–20	0
600–1700	20–60	6
1700–2800	60–100	12
over 2800	over 100	18

High serum potassium levels should be treated by promoting an increased urine flow, or, if this is impossible, by maintaining a high oral or intravenous glucose intake and thus causing glycogen deposition with a consequent movement of potassium ions from extracellular to intracellular fluid. Insulin injections may also be used to accelerate this process.

Acute Renal Failure and Renal Uremia. The regime described by Bull *et al.*[84] has proved successful in the management of acute renal failure following abortion or incompatible blood transfusion. A diet free from protein and electrolytes but containing 2500 cal in the form of arachis oil and glucose is given by intragastric drip. Only sufficient water is allowed to make good insensible and urinary losses. Any vomitus is filtered and returned down the tube. If well tolerated, such a diet will maintain fluid and electrolyte balance, minimize the rise of blood urea, and so give the kidneys time in which to recover; but patients are very liable to vomit or pass loose stools containing undigested fat. The author has found that tolerance is increased by giving the diet in two periods each of six hours, with six hours' rest between each, or by giving it as six single feeds at four hourly intervals. If still poorly tolerated, a high calorie, low protein diet should still be attempted by giving as much glucose, other sugars, or cream as possible. If cardiac or vena caval[88] catheterization is practicable, adequate caloric intake may be assured by infusing hypertonic glucose solution slowly into the great veins.

Experience with all these measures has, however, yielded poor results in acute renal failure and renal uremia following surgical procedures and head injuries, usually because the patients succumb within a few days before flow of urine can be re-established. Although death is often due to non-renal causes, the diets, even when well tolerated, never retard the rise of blood urea as effectively as they do after incompatible blood transfusion. This is possible because of the excessive protein catabolism of trauma and intercurrent chest or other infection, and raises the question as to whether high calorie, low protein diets can ever tide over the patient whose acute renal failure is caused by severe trauma for the length of time which the kidneys need to recover their function.

C. NUTRITION DURING REPAIR

As soon as there is evidence that the catabolic phase is ending, a high calorie diet rich in protein, vitamins, and essential minerals such as calcium and iron should be provided. The point of transition is often difficult to determine, but there is usually reduction of nitrogen excretion, a fall of blood urea concentration, and a marked desire on the part of the patient

to resume normal meals. Peters[27] advocates that "so long as the point of transition cannot be determined by any simple method it seems preferable to risk early extravagance . . . than to prolong parsimony into a period in which it may delay rehabilitation." He also emphasizes[74] that at this point every device that can stimulate appetite should be used, and that if the patient is weak he will often eat more if fed than if left to feed himself. The initially debilitated patient may be given high protein diets relatively earlier than one well-nourished, as the capacity to use protein anabolically is less markedly impaired. If there is post-traumatic anemia with hemoglobin concentration of less than 70 per cent, blood transfusion may be recommended.[11,56]

In unconscious patients, a high protein diet must be given by tube. Fluid diets which fulfil the necessary requirements are of two general types: milk fortified with eggs, glucose, and substances such as dried milk, predigested protein, and soya flour, and, secondly, normal meals whipped into fluid form in a homogenizer. The first type of diet, transition to which has been described after operation[5] and after head injury,[85] requires the addition of vitamin and iron supplements, but has advantages over the second; it may be easily and quickly prepared in bulk for several patients in amounts sufficient for 24 hours; its caloric and protein contents are known and may be easily varied, and it consists of readily digestible foods. It is important also to provide an adequate daily fluid intake (at least 3000 ml) during the period of high protein nasogastric feeding; otherwise azotemia, hypernatremia, and hyperchloremia may arise because of relative water deficiency.[86]

Conclusion

Although, diagnostically and therapeutically, increasing knowledge of the metabolic response to trauma is being successfully employed in saving life and shortening morbidity, patients may still succumb from injury, most usually from acute renal failure and irreversible shock. The most effective therapy at the physician's disposal, consisting mainly of replacement of fluid or other losses and the maintenance of a normal internal environment, is essentially negative, in that it submits passively to the metabolic demands of injury rather than actively attacking them. How much easier might not the general treatment of trauma be if local loss of fluid could largely be prevented, increased protein catabolism halted, or renal function preserved? To what extent, however, it might be argued, are these effects of trauma essential for the repair of damaged tissue, and might not their prevention cause sacrifice of the part in saving the whole? How badly needed, too, is a hypertensive drug that will at the same time promote renal vasodilatation? The solution of these and other problems lies in the field of laboratory research, for not until the mechanism of local fluid loss or increased protein catabolism is understood is their prevention likely to become possible, or prove therapeutically valuable. Since physical trauma is acquiring an increasingly important place among the hazards of modern life, it is much to be hoped that the answers to such questions will provide further therapeutic measures for combatting its general effects.

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Enlargement of the Parotid Gland in Malnutrition

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CHRONIC asymptomatic enlargement of the parotid and submaxillary glands has been observed in a number of countries. However, very few patients with this condition have been described in the American literature.[1] The present report describes the condition as seen among special groups in the United States and among certain Asiatic populations.[2] An attempt is made to relate the condition to the nutritional status of the population.

PREVIOUS OBSERVATIONS

During the past half century a chronic noninflammatory swelling of the parotid gland has been reported as occurring endemically in areas with limited food supplies. All races and age groups have been affected, and it appears to be more prevalent in areas of the world where the supply of animal protein is especially limited, that is, in the Far East and Africa. It was frequently observed in both the civilian population and repatriated prisoners of war in eastern Europe after both world wars. In the United States the parotid swelling has been reported only in association with chronic disease.

Sandwith[3] (1905) was among the first to describe an enlargement of the parotid gland which occurred endemically among the poorer agricultural workers in Egypt. The afflicted were generally unaware of its presence. He attributed it to a chronic parotitis, or to an obstruction of Stensen's duct. Fontoynont[4] reported that an asymptomatic chronic parotid gland enlargement known as "le mangy" was endemic in Madagascar. In some rural areas it occurred in 100 per cent of the population. The sexes were equally affected, but children two to four years of age seemed to be especially susceptible. He noted a familial pattern and a relationship to a poor dietary which consisted mainly of potatoes. Erlich[5] reported that during 1916 and 1917 large numbers of Polish children under 13 years of age had an enlargement of the parotid glands. She noted that the sexes were equally affected. A year later the percentage affected decreased. This she attributed to an improvement of the food situation. Miller[6] observed it frequently in mental patients and among the poor agricultural workers in Egypt and noted that it frequently occurred in association with pellagra. Kenawy,[7] again from Egypt, observed that a chronic bilateral enlargement of the parotid glands occurred in about two per cent of hospital admissions at two provincial hospitals in a district of poor agricultural workers. In 100 in-patients with the condition he found 65 to have an associated pellagra and 10 others to have diabetes. Ninety-three of the 100 patients with the enlargement were males, and most of them were between 20 and 40 years of age. Gillman and associates[8] in 1947 and Brock[9] in 1955 reported that enlargement of the parotid gland was comparatively common in malnourished Africans, and Davies[10] observed that the swollen glands developed during recovery from kwashiorkor.

During and following World War II a similar swelling of the parotid and submaxillary salivary glands was commonly seen in prisoners of war who had been repatriated from Russia. This abnormality was less frequently

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seen in the civilian population of eastern Europe. Bansi[11] mentions that at one period during the War his colleagues considered the possibility of the condition being "a new infectious disease," since the number affected increased to epidemic proportions. Kanther[12] studied the condition in repatriated prisoners of war and noted that the swelling appeared while the prisoners were undernourished and before their general condition had improved. McCance and his colleagues[13] observed that the swelling developed during the refeeding of the prisoners but then slowly subsided as the men regained metabolic equilibrium. The repatriated prisoners received as much as 1260 grams of bread and 7000 calories per day. The swelling became obvious by the end of the two or three weeks of refeeding. It was usually accompanied by obesity. They did not observe the enlargement in undernourished civilians or in civilian prisoners at the Siegburg jail. The gradual improvement in the food supply for the civilian population and the absence of any caloric debauchment was suggested as a possible explanation for the absence of parotid enlargement among the civilian population.

Takaoka, Yamaguchi, and Kosaka[14] cite colleagues who reported that many Japanese soldiers repatriated from Soviet war prison camps "suffered from an epidemic of mumps which showed no signs of fever, redness, or pain." In all of these studies the swellings developed in association with malnutrition or during the refeeding period.

Recently, S. V. Raja Rao and his associates[15] observed parotid enlargement in one to two per cent of the rural population of Mysore State in India. They also found an associated submaxillary salivary gland enlargement in a smaller percentage. This nutrition survey was conducted in 1950–53 and included about 35,000 people.

Response to "work" from ingestion of a high carbohydrate diet has been advanced as a cause of the glandular hypertrophy. This hypothesis has not been supported by studies of the rations and clinical condition of the Chinese Nationalist Army on Formosa. Pollack and associates[16] found only two cases with the enlargement in 1871 troops examined. Earlier, Ebbs[17] found in her study of the rations of this Army that the issue of rice was about 27 ounces (765 gm) per day, rice carbohydrate supplying up to 90 per cent of the total calories of the ration.

Despite the widespread occurrence of the parotid enlargement in areas of undernutrition, this condition was not reported in the nutrition surveys conducted by the Allied groups in Western Germany, the Netherlands,[18] Denmark,[19] Belgium, France, or Italy, after World War II. Neither was the syndrome reported in the nutrition surveys of 1945 in Indonesia[20] or in the studies on malnutrition at the Japanese prison camps in Singapore.[21] Further, a review of the literature fails to show that it has been observed in South America. However, Scrimshaw[22] reports that he has checked the records of the Instituto de Nutrición de Centro América y Panamá and finds that the condition is very rare in Central America, although he and associates at the Institute occasionally observe cases in children.

A number of investigators have reported the presence of a similar parotid gland enlargement in association with endocrine disorders, obesity, pregnancy, and in parasitic infestations. In the United States, one of the earliest reports of this condition was by John[23]. He reported four cases of a chronic bilateral parotid gland enlargement in women diabetics, all of whom were of European birth. Control of the diabetes, which was mild, did not affect the size of the gland. He diagnosed these as Mikulicz's disease, but in none of them was there an involvement of the lacrimal gland. Kenawy[7] found ten per cent of his patients with enlarged parotid glands to be diabetic. Takaoka and colleagues[14] found that 80 per cent of the 150 patients attending their diabetic clinic in Tokyo had enlarged parotids. Sprinzels[24] found gynecomastia in several of 33 obese male patients with the parotid enlargement.

The abnormality appears to be very prevalent in Japan. Takaoka and associates[25] found that 15 per cent of 2276 "normal" individuals were affected. He did not indicate

whether the group studied attended the clinic as patients or were representative of the general population. The condition was found in 35 per cent of high school girls and in 43 out of 44 women in the latter half of pregnancy. Kanther[12] found the parotid swellings in 21 patients with inanition dystrophy. In two of these cases there was an associated swelling of the submaxillary salivary glands and in six others an associated gynecomastia. None of the cases presented signs of an inflammatory process. Nash and Morrison[1] reported a case of bilateral asymptomatic enlargement of the parotid glands complicated by severe cardiospasm of 19 years' duration. In this case, generalized uniform dilatation of the tubules was demonstrated by sialogram without any direct evidence of a duct blockage. A biopsy of the parotid showed a very dense parenchyma with normal-appearing acini and ductules. In this case, there was a mild diffuse infiltration with lymphocytes in the paraductule tissues.

Marsden[26] studied 60 cases of "mixed" salivary tumor at the Institute of Medical Research, Federation of Malaya. The submaxillary gland was the site of the neoplasm in 30 per cent of the group. He cites an unpublished report of a colleague at the Institute, in which school children from an impoverished area were examined for enlarged parotid glands. The incidence among these children, by race, was: Malayan 20, Chinese 10, and Indian 5 per cent. Both sexes were equally affected. Marsden observed further that the enlargement persisted into adult life and in certain instances became permanent. He postulates that natives with chronic enlargement of the salivary gland resulting from malnutrition are predisposed to develop a tumor of the salivary gland.

More recently, Polunin,[27] in a survey of the aboriginal tribes of Malaya, found enlargement of the parotids in 68.9 per cent, visible in 33.1 per cent, of 653 aborigines. No difference in incidence was found between the sexes. In these people the enlargement occurred between the ages of one and five years and persisted almost unchanged until old age.

Gounelle[28] observed the development of a bilateral noninflammatory swelling of the parotid glands in three cachetic patients with bacillary dysentery. The swelling became apparent in 30, 42, and 75 days after the onset of illness, and regression was observed at 30, 50, and 60 days, respectively, after recovery from the dysentery.

The studies cited above include histopathological findings on single or, at the most, a very few cases. This perhaps accounts for the differences in the pathological description of these tissues. There is general agreement that it is not an inflammatory process. Gillman and associates[8] were "impressed by the great enlargement of the individual tubules or acini, so that in section there appear to be very large numbers of acini with extremely few excretory ducts. These acini are crowded with secretory granules which invariably stained intensely with haematoxylin and eosin preparations." McCance and colleagues[13] compared a specimen, obtained post mortem from a man who had very swollen parotids during life, with 14 apparently normal parotids obtained at necropsy and found no definite histopathological abnormality of the enlarged parotid. There was no trace of inflammatory cellular infiltration or fibrosis, and the adipose tissue was within normal limits. He concluded that the increase in size of the gland must be due either to an increase in size of the acini or to an increase in their number, or both. From his measurements, it appears that the enlargement of the parotid was due, at least in part, to an enlargement of the individual acinus.

Material and Method

The data on which this report is based include the results obtained in three surveys. One of the surveys was made on an Asian population[2] and the others on three hospital groups in the United States.

Description of Methods Used in Survey of Asian Group

The survey of this group consisted of a clinical appraisal for the detection of the major nutritional diseases, laboratory determinations that could be adapted to field work, and a review of the dietary. The number of per-

sons tested for each of these procedures varied from group to group.

The study on the Asian population was directed toward an evaluation of the nutritional status of the people. This study was made during the summer of 1953, when over 3100 subjects were examined. The records secured in that study are used only for the purpose of elucidating the nature of the parotid abnormality.

Some of the characteristics of the Asian population were as follows: All were males 15 to 53 years of age; both military and non-military groups were represented; physical activity varied from sedentary to heavy labor. For the military personnel the dietary intake was restricted to that provided by the army mess. In most cases the approximate period on the rations was known; the period extended from one day to three years.

The laboratory tests included the determination for plasma protein, hemoglobin, and hematocrit by the copper sulphate method described by Phillips and associates,[29] plasma ascorbic acid by modified method of Mindlin and Butler,[30] and vitamin A and carotene by the modified method of Dann and Evelyn.[31] Blood samples were collected from non-fasting subjects in the morning. The plasma to be used for the vitamin analysis was quick-frozen in a dry ice-alcohol mixture and air-lifted to a central laboratory.

Physical examinations were made in daylight with the subjects disrobed except for shorts; shoes and socks were removed.

The subjects were classified[2] into four groups on the basis of the relation of their weight to their height. Those whose weight was 90–110 per cent of "standard" were classified as normal; those over 111 per cent were considered overweight; those 80–89 per cent were considered moderately underweight; and those 60–79 per cent of the "standard" were classified as severely underweight.

The dietary appraisal consisted of obtaining information on the foods issued from a central source for a 30-day period. From the quantities of food issued and the average strength of the unit, food consumption for the individual was calculated. The nutrients provided per man per day were then calculated, using the values contained in U. S. Department of Agriculture Handbook No. 34—"Composition of Foods Used in Far Eastern Countries"[32] and the book "Standard Tables of Food Composition in Japan."[33]

Description of Methods Used in Survey of Two Hospital Groups in the United States

The hospital studies were directed primarily to determining the incidence of the parotid enlargement in groups that, because of their special circumstances, seemed most likely to show the condition. These surveys included an examination of the head and neck of 1094 adult mentally ill patients at Saint Elizabeths Hospital, District of Columbia, during January–March 1954, and a similar survey of 165 adult patients in three hospitals for American Indians in the Southwest during September 1954.

The patients at Saint Elizabeths Hospital were all ambulatory, chronically ill from mental disease and, with a few exceptions, were co-operative. All were able to go to the dining room and feed themselves. The period of residence in the institution ranged from one to 40 years. The age range of those examined was 18–80 years.

The 1094 patients studied at Saint Elizabeths Hospital represent about one-seventh of the total hospital population. The sample is not representative of the total population because all available patients of Asian, Philippine, and American Indian extraction were included (Table I). The Indian patients were from seven Indian tribes, all from the Midwest or Southwest. These included the Apache, Cherokee, Navajo, Papago, Pima, Pueblo, and the Sioux. There were 512 white and 505 Negro patients in the study, most of whom had been admitted to the hospital from the District of Columbia or nearby Virginia or Maryland.

The other hospital groups examined were patients at the Indian Service and Mission hospitals. These included Apache, Cocopah, Maricapa, Navajo, Papago, and Pima tribes. There were 32 examined at the Presbyterian Mission Hospital at Ganado, New Mexico, and

124 at the Indian Service hospitals at Phoenix, Arizona, 94 of whom were patients at the tuberculosis sanatorium and 30 of whom were in the general hospital.

In all of the studies, confirmation of the presence of an abnormally enlarged parotid gland was made by at least two physicians.

TABLE I

Enlargement of Parotid Gland, Saint Elizabeths Hospital, Washington, D. C. January–March, 1954.

	Male			Female		
Group	No. Examined	Pos.	%	No. Examined	Pos.	%
Indian	23	8	35.0	39	10	26.0
Negro	254	10	3.9	251	2	0.8
White	265	0	0	247	2	0.8
Chinese*	3	2	66.6	1	1	100.0
Filipino*	10	4	40.0	0	0	0
Puerto Rican*	1	0	0	0	0	0
Total	556	24	4.3	538	15	2.7

* Foreign born.

Observations Relative to Parotid Enlargement in the Group Studied

Results of Surveys—Frequency and Duration

An estimate of the frequency of an asymptomatic enlargement of the parotid gland in special groups in the United States is shown in the survey of patients in hospitals for the mentally ill and in hospitals restricted to the care of the American Indian.

Among the patients at Saint Elizabeths Hospital, the parotid enlargement occurred in 39 (3.5 per cent) of 1094 patients examined (Table I). Three of the four Chinese and four of the ten Filipinos had the condition. Eighteen of the 62 American Indians were affected. It was found in only two of 512 white patients and in 12 of 505 Negro patients. Both sexes were affected; however, it appeared to be slightly more frequent in the males.

The survey of the patients in the three Indian hospitals indicates that the condition is relatively frequent in American Indians of the Southwest. Twenty (12 per cent) of the 165 patients examined were affected. The condition was more common in the male than in the female; 14 (20 per cent) of the 69 males had the condition as compared to six (6.2 per cent) of the 96 females.

In the survey of the Asian population the abnormality was frequently found in a group in which it had not been previously recognized. In this adult male population (military and nonmilitary) it was observed in 369 (11.6 per cent) of 3168 persons examined.

The duration of the enlarged parotid could not be determined in the American groups. A review of the hospital records at Saint Elizabeths failed to show whether it had been previously seen. It is probable that the condition existed prior to admission since full-face photographs taken at that time showed many to have an abnormal fullness in the parotid area. Neither was there any information at the hospitals for the Indians which would assist us in determining how long the condition had existed.

In the Saint Elizabeths and Indian hospital populations it was found in both young adults and the elderly, the youngest being 18 years and the oldest 72 years of age.

Clinical Features

The swelling of the parotid gland was usually bilateral and symmetrical with all lobes affected. When the swelling was marked, the ear lobules were hidden from front view (Figs. 1, 2, and 3). The glands were soft to moderately firm; they could be readily outlined. The glands tended to be more firm in the Asian group than in the patients in American hospitals. There were no complaints referable to the gland; it was not tender to palpation. None of the subjects was aware of its presence. The subjects were afebrile, and there was no other evidence of an inflammatory process. The mucosa of the mouth, including the ampulla of Stensen, appeared normal, and there was no apparent dysfunction of salivation.

In the Far Eastern group, the submaxillary salivary glands were bilaterally enlarged in about 10 per cent of the individuals with the enlarged parotid glands (Fig. 4). The submaxillary glands were not found to be enlarged in the American group.

Fig. 1. Asian male with bilateral enlargement of parotid glands, which hides the ear lobules from front view. Also note the bilateral angular cheilosis.

Fig. 2. Lateral view to show method of palpation of the gland.

Fig. 3. Rear view to show postauricular swelling of the parotid which may push the ear forward and cause a flaring of the lobules.

Fig. 4. Showing enlargement of both the submaxillary gland and the parotid.

Laboratory and Pathological Findings

Thiocyanate Content of Saliva

The estimation of thiocyanate content of the saliva was used as a measure of parotid function. Specimens were collected from 15 affected patients at Saint Elizabeths and from eight staff members. The specimens were collected at least two hours after breakfast, using the method described by McClure.[34] The method of Saunders[35] was used to determine thiocyanate content.

The concentration of thiocyanate in the saliva collected from 15 patients with parotid enlargement at Saint Elizabeths Hospital was 20.3 mg per 100 ml (expressed as KCNS). The group of eight normal individuals with no signs of parotid enlargement had 20.6 ± 5.8 mg per 100 ml. In both groups the values ranged from a concentration of 1.5 mg to approximately 50 mg per 100 ml. To the extent that thiocyanate concentration reflects functional activity of the parotid gland, there appears to be no difference in individuals with enlarged and those with normal glands.

Tissue Culture of Parotid Gland

The tissue culture method was used to evaluate the viability of the epithelium and possible presence of cyto-pathogenic virus. Biopsy specimens were obtained from five affected patients at Saint Elizabeths Hospital, and studied by W. P. Rowe of the National Microbiological Institute. His report follows: "Roller tube tissue cultures were prepared using the technique and modified Enders medium described by Rowe, Huebner, Gilmore, Parrott, and Ward.[36] Four of these tissues grew well in culture, with excellent growth of epithelial sheets. The cultures were observed for periods ranging from thirty-four to one hundred and two days, and no evidence of degeneration suggestive of virus activity was seen."

Pathologic Findings

During the course of this study, parotid glandular tissue was examined histologically from three male Asian patients who had enlargement of the parotid gland. Their ages varied from 23 to 32 years and one patient was known to have had bilateral parotid enlargement for two years (Figs. 11 and 14). The duration of parotid enlargement is unknown in the other two patients. In each subject the fragment of tissue obtained was about 1 cm in greatest diameter, was soft, and consisted of lobular tissue with no unusual gross features. The specimens were fixed in 10 per cent formalin solution. Parotid glandular tissue also was available from two other subjects in the Far East. One of these was a healthy, 22-year old male American Negro soldier who suffered accidental death. This patient did not have parotid enlargement. Glandular tissue was obtained at autopsy and fixed in 10 per cent formalin. The other was an Asian male of unknown age from whom tissue was obtained at autopsy. This patient did not have parotid enlargement.

In addition, parotid glandular tissue obtained by biopsy from five patients with parotid enlargement at Saint Elizabeths Hospital, Washington, D. C., was also used in this study. This tissue was fixed in formalin-corrosive sublimate. These patients were two Chinese males (foreign-born), two American Negro males, and one American Indian, whose ages ranged from 38 to 54. No abnormal gross changes were noted in the parotid either at

Figure 5

Figure 6

Figure 7

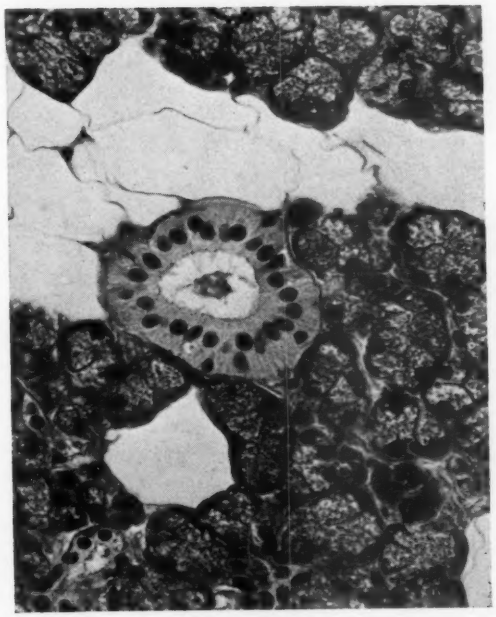

Figure 8

Figs. 5, 6, 7, 8. Parotid glandular tissue from three Saint Elizabeths Hospital patients showing abundant intralobular fat. Figs. 5, 6, (×20); Figs. 7 (×20) and 8 (×400) are from the same case.

Fig. 9. Parotid glandular tissue from Asian patient with clinically enlarged gland (×20).

Fig. 10. Higher magnification of tissue from case shown in Figure 9 (×400).

the time of surgery or when examined in the pathology department.

Thus, tissue was available for microscopic study from ten patients, eight of whom had parotid enlargement clinically. Study of this tissue failed to reveal diffuse fibrosis, chronic inflammation, or obstruction of the excretory ducts which would explain the clinical finding of parotid enlargement. Intra-parotid lymph nodes were not included in any of the specimens. However, several microscopic features are of interest.

The first is that there is abundant intralobular fat in the parotid glandular tissue of the Saint Elizabeths Hospital group of patients (Figs. 5, 6, 7, and 8). The size of the serous cells, the acini, the number of zymogen granules and the ducts all appear within normal limits (Fig. 8). It is possible that the parotid gland enlargement in these cases may be due to fatty infiltration. However, this amount of intralobular fat may not be abnormal because the amount of fat tissue seen within presumably normal parotid glands is quite variable, and even in this material the amount of intralobular fat varies considerably in various lobules (Fig. 6).

Microscopic examination of the material from the Asian patients with enlarged parotid glands reveals enlarged parotid lobules with minimal intralobular fat (Figs. 9, 11, and 13). The enlargement of the lobules appears in part due to enlargement of the individual serous cells, which resembles the case described by McCance.[13] Compare the size of acinar cells and acini in Figures 10, 12, and 14 with Figure 8. These photomicrographs are taken at the same magnification. The difference in cell size is particularly evident if one compares the number of nuclei in a given area of the photomicrographs of Figures 10, 12, and 14 with the number of nuclei seen in Figure 8. The acinar cells in these Asian patients contain variable amounts of zymogen material and in some areas the cell cytoplasm is markedly vacuolated. The parotid tissue which shows the most marked degree of vacuolization (Figs. 13 and 14) was obtained at autopsy, and the details of time of fixation after death are not known. Examination of Figure 13

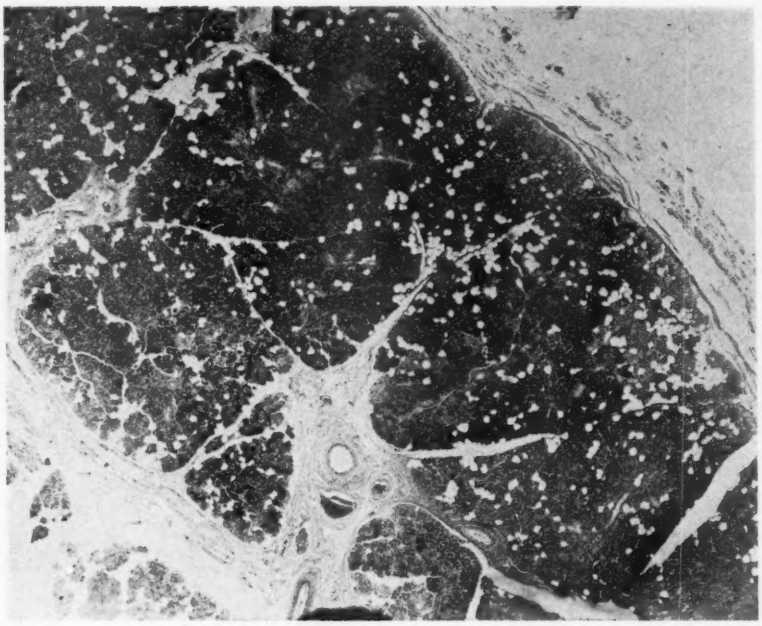

Fig. 11. Parotid glandular tissue from Asian patient with clinically enlarged gland (×20).

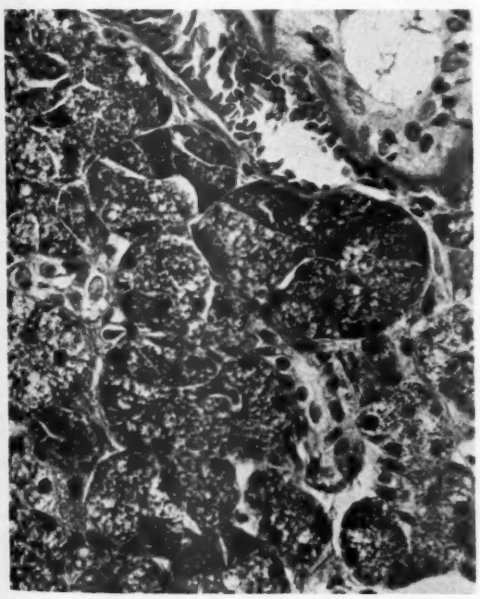

Fig. 12. Higher magnification of tissue from case shown in Figure 11 (×400).

reveals that the most marked areas of cytoplasmic vacuolization are on the periphery of the lobule and this is thought to be in part artefact. However, increase in acinar cell size and moderate vacuolization of cytoplasm is also seen in sections from the other two Asian patients with enlarged glands (Figs. 10 and 12), and tissue from these patients was obtained surgically and immediately fixed in formalin. This material resembles that reported by Kenawy[7] who obtained parotid tissue from three post mortems and two biopsies. The weights of the postmortem parotids were two to four times those found in normal specimens. He considered the change to be a hyperplasia, noting that the histologic appearance varied greatly and was almost normal in material obtained at biopsy.

Study of the parotid glandular tissue from the American Negro soldier and the other Asian male who did not have parotid enlargement revealed minimal to moderate amount of intralobular fat and small acini and acinar serous cells.

Thus, study of this material fails to reveal a common pathological change which would explain the clinical finding of parotid gland enlargement in these two groups of patients. The histologic appearance of the glands of

Fig. 13. Parotid glandular tissue from Asian patient with clinically enlarged gland (×20).

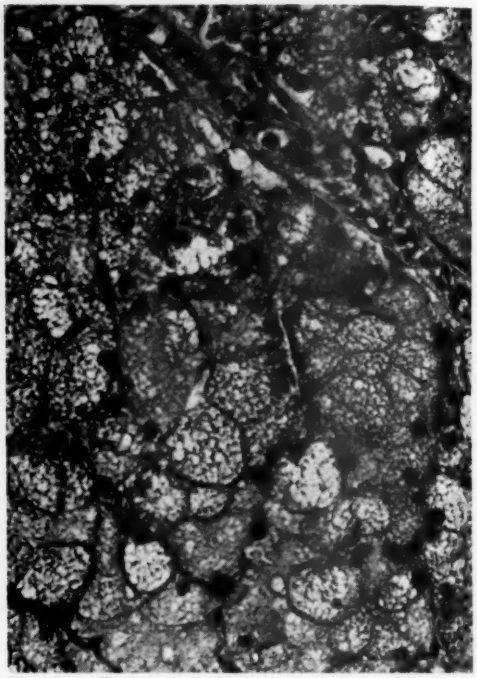

Fig. 14. Higher magnification of tissue from case shown in Figure 13 (×400).

the Saint Elizabeths Hospital group of patients is quite similar from case to case, and the only apparent cause of gland enlargement is intralobular fatty infiltration. This does not explain the enlargement of the glands in the Asian patients, because the amount of intralobular fat in their parotid tissues is minimal. The only apparent explanation histologically of enlarged glands in these latter cases is enlargement of acinar cells.

However, such material as was available for examination in this study is considered inadequate to determine definitely the pathogenesis of the glandular enlargement in these patients. It would seem necessary to obtain both parotid glands and determine their weight and fat content before definite conclusions can be drawn concerning fatty infiltration or hyperplasia or hypertrophy of acinar cells.

Associated Conditions in the American Group

The literature cited refers to several reports in which the abnormality was found in association with various chronic diseases. In the Saint Elizabeths group there were nine patients with histories of epilepsy and four with diagnoses of diabetes. Except for enlargement of the parotid glands, this group of 39 patients did not appear to be physically different from their fellow patients; a few were excessively overweight. In the Southwest Indian group, the percentage affected was considerably higher in the general hospitals than in the sanatorium. Thirteen (18.3 per cent) of the general patients had the condition, and seven (7.3 per cent) of 94 patients with tuberculosis. Only one of the 165 patients was diabetic, and there was no epilepsy. In neither group were there patients with gynecomastia or with an associated disturbance of the lacrimal gland upon which a diagnosis of Mikulicz's syndrome could be made.

Observations Relative to the Nutritional Status of the Group Studied

Studies of Data in Nutritional Survey of Asian Population

If, as suspected by several investigators, the parotid swelling is a manifestation of malnu-

trition, the data collected in a nutrition survey of an Asian population where the condition is endemic might offer some clues as to its pathogenesis. Since the diet was deficient in several nutrients, it was not possible to relate the parotid abnormality to a specific food factor. However, if the condition was found to be frequent in individuals with clinical signs of a specific deficiency, some indication as to its causation might be secured. Fortunately, a number of factors which influence the development of nutritional disease are known in this survey. The case rates in the population may be studied in relation to age, body weight, exposure time to a deficient diet, other physical signs of nutritional deficiency disease, and to the blood chemistries. The field conditions, unfortunately, did not permit the testing for therapeutic effectiveness of nutritional supplements.

TABLE II

Distribution of Cases with Parotid Hypertrophy by Age Group and % Standard Weight—Asian Population

% Std. Wt.	Age group														
	Under 20			20–24			25–29			30 and over			All ages		
	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%
111% and over	0	0	—	29	7	24.2	31	2	6.5	35	4	11.4	95	13	13.7
90–110	47	5	10.6	579	79	13.6	643	73	11.3	253	25	9.9	1522	182	11.9
80–89	25	2	8.0	249	52	20.8	292	40	13.7	47	4	8.5	613	98	16.0
60–79	1	1	100.0	44	18	41.0	13	1	7.0	2	0	0	60	20	33.3
Total	73	8	10.9	901	156	17.3	979	116	12.0	337	33	9.9	2290	313	13.7

Summary of Dietary Evaluation of the Asian Population

The dietary intake[2] was inadequate[37,38] in respect to calories, fat, vitamin A, thiamine, riboflavin, and ascorbic acid, and secondarily in respect to protein when it was compared to recommended allowances. The amount of food issued to the groups varied considerably. There were marked differences in the amount of energy expended by the different groups, but within a group all of the individuals received approximately the same quantity of food. The daily calorie intake ranged from 2900 to 3965. This amount of energy was adequate for sedentary and moderate activity, but was inadequate for heavy work as judged by body weight. The protein intake ranged from 70 to 110 grams and was considered adequate except in those groups receiving inadequate calories. The fat intake was very inadequate and ranged from a low of 12 grams for some groups to 28 grams in more favored groups. This low fat intake probably raised the dietary requirement for vitamin A and thiamine. Vitamin A intake was inadequate[39] for all groups, providing as little as 485 IU daily to one group of men. The thiamine intake ranged from 1.09 to 1.3 mg and was considered inadequate[40] at the lower level when physical activity was heavy. Riboflavin intake was inadequate[41] for all groups, ranging from 0.57 to 1.1 mg daily. Niacin intake ranged from 15.6 to 34.8 mg and was considered adequate. The ascorbic acid intake varied with the seasons, but was inadequate[42] much of the year. The daily intake of this nutrient during a two-months period when this survey was made ranged from a low of 3.2 mg for one group to 58.4 mg daily for a more favored group.

Relation to Age Group

The relative frequency of parotid hypertrophy was computed for each of four age groups (under 20 years, 20–24, 25–29, and 30 and over). Detailed examination of the population sub-groups which made up the totals given in Table II did not show any consistent age trend. Depending on the sub-group examined, the highest frequencies of parotid enlargement occurred in the youngest men,

the oldest men, or in either of the intermediate groups. This absence of relation of age to body weight or the occurrence of other signs of nutritional deficiency was also noted.

Relation to Time on a Deficient Diet

There was not a sudden or rapid increase in the proportion of persons with enlarged glands, as might occur in an epidemic of infectious parotitis. Where it occurred, the condition developed slowly over several weeks. From then on, the incidence increased until it reached a peak of 56.4 per cent after 6 to 8 months. The incidence of parotid enlargement was only 2 per cent among 507 men prior to exposure to the deficient diet. After 4 to 5 months on the deficient diet, it rose to 31 per cent. Men who had been on a slightly better diet for one and a half years showed an incidence of 38 per cent. This apparent decline (from the peak of 56.4) may have resulted from a better dietary, since the men were less active and had been issued about 3965 calories per day. Fewer of this latter group were underweight or showed signs of nutritional deficiencies.

Relation to Calorie Deficiency

If it is accepted that deviations from "standard" body weights are related to the degree of caloric restriction, then Table II indicates a positive but not necessarily causal relation of the parotid swelling to caloric deficiency. In the group with body weights that were 111 per cent or more of the "standard" weight, the incidence was 11.9 per cent; in the normal weight group (90 to 110 per cent of "standard") the incidence was 13.7 per cent. In the moderately underweight (80 to 89 per cent of "standard") the incidence was 16.0 per cent, while in the severely underweight group (60 to 79 per cent of "standard" weight) it was 33.3 per cent.

Relation of Signs of Thiamine Deficiency to Parotid Hypertrophy

Calf muscle tenderness,[43] a presumptive sign of thiamine deficiency, varied in frequency from 3.5 to 41 per cent in the population and was often accompanied by other clinical signs of the deficiency. There is some relationship of the calf tenderness to the parotid enlargement in that 27 per cent of the individuals with calf tenderness also had the parotid enlargement, whereas only 12.5 per cent of those without the calf tenderness had the enlargement.

Relation of Parotid Hypertrophy to Pellagroid Pigmentation and Angular Cheilosis

In an examination of non-white people it is at times difficult to assess changes in pigmentation of the skin over that which might normally occur as a result of sun tanning. An attempt was made to record those individuals with an abnormal pigmentation[2,44] which resembled pellagrous dermatitis.[45] When the results of the examinations of all individuals were combined, there appeared to be a very strong association between the pigmentation and the parotid hypertrophy (Chi-square was 133.5 with one degree of freedom). Eighteen per cent of the persons with the pellagroid pigmentation had parotid enlargement, whereas only 5 per cent of persons without pellagroid pigmentation had the glandular enlargement. This would seem to indicate that these two conditions were closely associated.

Angular cheilosis,[46] a sign associated with riboflavin deficiency, was one of the most frequent abnormalities found. There was a significant relationship between the hypertrophy and the angular cheilosis. Twenty per cent of the 1126 individuals with an acute angular cheilosis had parotid enlargement, whereas only 8.7 per cent of the individuals without the cheilosis had the parotid abnormality (Chi-square 89.9).

Since both angular cheilosis and pellagroid pigmentation appeared to be associated with the glandular enlargement, the data were examined to determine whether there was any association when the groups were combined. When angular cheilosis and pellagroid pigmentation are compared they were found to be independent of each other (Chi-square 1.89). The test was applied to 1535 indi-

viduals of comparable status (Table III). Thirty-seven per cent of the individuals with angular cheilosis and pigmentation in combination also had parotid enlargement, whereas only 5.5 per cent of the individuals with neither the angular cheilosis nor pigmentation had the hypertrophy.

TABLE III

Association of Angular Cheilosis and Pellagroid Pigmentation to Parotid Hypertrophy—Asian Population

Associated condition	No.	All persons (%)	Parotid hypertrophy	
			No.	%
Pell. Pig. Positive Ang. Cheil. Positive	456	29.8	168	36.8
Pell. Pig. Positive Ang. Cheil. Negative	458	29.8	65	14.2
Pell. Pig. Negative Ang. Cheil. Positive	240	15.6	18	7.5
Pell. Pig. Negative Ang. Cheil. Negative	381	24.8	21	5.5
Total	1535	100.0	272	17.8

Pell. Pig. = pellagroid pigmentation.
Ang. Cheil. = angular cheilosis.

Relation to Anemia

Persons with anemia appear to have the parotid abnormality more frequently than the non-anemic individual. This is shown by the data on 604 individuals on whom hemoglobin determinations were made. Parotid enlargement was found in 9 of 34, or 26.4 per cent, of the group below 12 gm hemoglobin per 100 ml; in 36 of 187, or 19.3 per cent, in the 12.0–13.9 gm range; in 33 of 376, or 8.8 per cent, in the 14.0–16.9 gm range; and in one of 7 subjects in the hemoglobin range above 17 gm per 100 ml.

Relation to Hypoproteinemia

In the Asian group, plasma proteins were determined on 611 subjects, 117 of whom had enlarged parotid glands. The data indicate a significant relationship of hypoproteinemia to the parotid swelling. Table IV shows the distribution of positive cases by plasma protein level. Of the subjects with plasma protein levels below 7.00 gm per 100 ml, 31.2 per cent had the abnormality, whereas only 16.6 per cent of the group with levels between 7.00 and 8.49 gm per 100 ml had enlarged glands. A small group of 21 subjects with excessively high plasma protein values had the parotid abnormality in one-third of their number. Six of the seven individuals in this latter group with parotid hypertrophy were in one sub-unit.

TABLE IV

Distribution of Cases of Parotid Hypertrophy by Level of Plasma Protein—Asian Population

Plasma protein gm/100 ml	Total	Positive	%
Less than 6.00	22	8	36.2
6.00–6.49	28	8	28.7
6.50–6.99	33	10	30.3
7.00–7.49	269	49	18.2
7.50–7.99	157	26	16.6
8.00–8.49	81	9	11.0
8.50 and over	21	7	33.0

Relation to Ascorbic Acid and Vitamin A Plasma Levels

Vitamin A and ascorbic acid plasma levels reflected the dietary intake of these nutrients and were in good agreement with the clinical findings. The records of 297 individuals who had determinations for vitamin A were studied in respect to the parotid gland enlargement. The plasma levels of the vitamin A were grouped in three ranges: severe depletion, 0–9.9 μg per 100 ml; moderate depletion, 10.0–25.0 μg; and satisfactory, 26.0 μg and over. There was no positive relation of the degree of vitamin A depletion to the parotid abnormality. The percentage of positive cases in each range was 25.0, 20.5, and 25.0, respectively.

Determinations for plasma ascorbic acid levels were made on 316 individuals. Unsatisfactory plasma levels, below 0.20 mg per 100 ml, were found in 187 individuals, 15.5 per cent of whom had enlarged glands. In the group of 129 individuals with satisfactory plasma levels (above 0.20 mg per 100 ml), there were 53 (or 41 per cent) with the parotid enlargement. No explanation was found for the higher plasma values in the group with the parotid enlargement.

Summary

An enlargement of the parotid gland occurs relatively frequently in the United States among groups, who, because of special circumstances, are susceptible to nutritional difficulties. The condition was found in 12 per cent of 165 Indian patients in hospitals in the Southwest and in 3.5 per cent of 1094 patients examined at Saint Elizabeths Hospital, Washington, D. C. It was found more frequently in the foreign-born Oriental and American Indian patient than in the Negro or white patient. Whether this was due to a geographical influence was not determined.

The results of the study of the Asian population support the observations of other investigators that the condition is widespread among populations of limited food supply. The enlargement appears to be a manifestation of a chronic and possibly severe form of malnutrition. The dietary factor or factors involved were not identified; however, the condition occurs most frequently among subjects who presented multiple signs of deficiency. These included underweight, pellagroid pigmentation of the hands and face, angular cheilosis, calf tenderness, anemia, and hypoproteinemia.

It was found in 12 per cent of those in normal and above normal weight range, in 16 per cent of the moderately underweight, and in 33 per cent of the severely underweight.

There was a highly significant relationship of the condition to angular cheilosis and pellagroid pigmentation when these conditions were both present. In the group that had both of these conditions it was found in 36.8 per cent of the persons, whereas in the group which had neither of the conditions it occurred in only 5.5 per cent. A similar relationship was found with respect to anemia and calf tenderness.

Relationship of the abnormality to the adequacy of ascorbic acid and vitamin A nutrition was not demonstrated. Neither was a relationship to the age of the individual demonstrated. Perhaps this was due to the narrow age spread (18 to 35 years) of the majority of the group.

The condition was relatively slow but progressive in development. It was observed that when subjects who were initially at a marginal nutritional state were maintained on a diet deficient in several nutrients, the condition developed within two to four months, reaching a peak incidence at six to eight months, thereafter subsiding in frequency as the dietary conditions improved.

There does not appear to be an inherent racial characteristic which favors the development of the condition. The incidence was high among Caucasian prisoners of war and concentration camp victims in eastern Europe after both World Wars, but was not observed in the nutrition surveys conducted in western Europe.

The pathological and tissue culture studies support the clinical impression that the condition is noninflammatory. The enlargement in the acute phase appeared to be due to a swelling of the individual cells and in the chronic phase to a replacement of acinar tissue with fat. Persons who had had the condition for several years showed no disturbance of the secretory function of the gland, as indicated by thiocyanate tests.

The Saint Elizabeths Hospital data suggest that the condition found in well-nourished individuals may represent residual hypertrophy after recovery from malnutrition.

Populations who were previously well nourished[18,19] appear to be resistant to its development during relatively short periods (4–6 months) of privation. Populations subsisting on a marginal diet appear to be highly susceptible and develop the abnormality within four months when the diet becomes sufficiently restricted in calories, proteins, and vitamins of the B complex to produce clinical signs of these deficiencies.

Conclusions

Data are presented which support the observations of several investigators that a bilateral chronic asymptomatic swelling of the parotid gland is a manifestation of recent or remote malnutrition. It is probably worldwide in distribution but occurs most frequently in populations subsisting on diets

which are chronically inadequate. In this study it was found associated with underweight, hypoproteinemia and anemia, angular cheilosis, calf tenderness, and pellagroid pigmentation. The presence or absence of this abnormality should be noted in all physical examinations and its significance determined, including a nutritional history and biopsy if indicated.

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The Human Requirement for Iodine

By Isidor Greenwald, ph.d.*

This paper presents no new experiments but rather is the result of an attempt to evaluate the available evidence as to the amount of iodine required by human beings. This subject will be discussed in the following order: I, the excretion of iodine during fasting; II, studies of equilibrium; III, the usual excretion in regions in which goiter is frequent and in those in which it is unusual; IV, the results of experiments upon animals; V, the amount used to lessen the incidence of goiter.

I. Excretion of Iodine during Fasting

There seem to be but few determinations of iodine excretion during a fast (Table I).

TABLE I

Excretion of Iodine while Fasting

Author	Number of days	Excretion per day	Footnotes*
		μg	
v. Fellenberg[2]	2	23	(1)
v. Fellenberg[2]	2	38	(2)
Boe and Elmer[3]	1	14	(1,3)
Flickinger[1]	6	76	(4)

*Footnotes: (1) Urine only. (2) Includes feces, nasal mucus, and sweat. Experiment performed three days after a period of augmented intake of iodine. (3) A twelve-hour night specimen contained 12 μg. (4) Includes urine, sweat, and feces. Almost certainly too high. See text.

The value of 76 μg per day reported from Flickinger's experiments[1] is almost certainly too high. It includes 35 μg supposedly present in the feces. However, no feces were passed during the fast and the value of 35 μg was obtained by pro-rating the total amount of iodine in the feces passed during the following three days. Since the total fecal iodine for the nine days (six of fast and three of feeding) was much greater than in any similar period in which food was taken daily, it would seem that there was a gross error in the analysis.

On the other hand, the urinary iodine in the second three-day period of fasting was 58 μg, or 19 μg per day, which is in fair agreement with the values reported by v. Fellenberg[2] and by Boe and Elmer.[3]

II. Studies of Iodine Equilibrium

Table II presents a summary of the results of studies on equilibrium or "balance." Even if we disregard the figures reported by McClendon and Hathaway[4] and some of those reported by v. Fellenberg,[2] which may be too low, it would appear that equilibrium was readily attained with about 50 μg of iodine per day and that even slightly higher intakes may lead to retention. Presumably, such higher intakes eventually lead to equilibrium at a higher level, just as is the case with nitrogen, phosphorus, calcium, and so on. Some of Flickinger's results (Table II) may indicate a slightly higher requirement than 50 μg but these higher values for the amount of iodine in the excreta may reflect, as in the first experiment upon subject J (see footnote 7), a high intake before the observations were begun. (A person who has been on a diet containing 20 gm of nitrogen will not come into equilibrium on a diet containing only 10 gm of nitrogen until several days have elapsed.)

III. Usual Excretion in the Urine

In Table III there are presented what seem to be the significant figures, as reported in 23 different papers by fifteen different sole or senior authors. The data have been arranged in approximate chronological order, deviating from this in order to bring together those reported by the same investigator or

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TABLE II

Studies of Iodine Balance

Author	Subject	Sex	Weight kg	No. of days	Iodine in Food and Drink µg.	Iodine in Excretion µg.	Balance µg	Footnotes* (1)
v. Fellenberg[2]	A	M	—	3	14.3	14.4	−0.1	(2)
v. Fellenberg[2]	A	M	—	4	14.3	12.4	+1.9	(3,3A)
v. Fellenberg[2]	A	M	—	8	53	35	+18	(3,3B)
v. Fellenberg[2]	A	M	—	12	72	51	+21	(3,3C)
McClendon & Hathaway[4]	B	M	—	3	19	7	+12	(4)
Scheffer[5]	C	M	—	3 or 5	131	105	+26	—
Scheffer[5]	D	M	—	3 or 5	54	53	+1	—
Scheffer[5]	E	M	—	3 or 5	54	50	+4	—
Scheffer[5]	F	F	—	3 or 5	59	41	+18	(5)
Puppel & Curtis[6]	G	M	56	15	156	74	+82	(4,6)
Puppel & Curtis[6]	H	F	49	15	56	44	+12	(4,6)
Flickinger[1]	I	M	68	6	33	64	−31	—
Flickinger[1]	J	M	59	9	24	71	−47	(7)
Flickinger[1]	J	M	59	6	551	434	+117	—
Flickinger[1]	K	F	65	9	32	75	−43	(8)

* Footnotes: (1) All figures are *per day*. Unless otherwise indicated, the values for the iodine excreted include that in urine, feces, and sweat. (2) Urine only. (3) Excretion includes that in nasal mucus. (3A) 1.5 gm thymol ingested daily. (3B) 50 µg KI added to regular diet. (3C) Regular diet plus cod liver oil (6 days), sardines (3 days), watercress (2 days) and 50 µg KI (1 day). (4) Does not include loss in sweat. (5) Does not include loss in sweat but does include 10 µg supposed to be lost in breath. (6) All foods known to be rich in iodine (sea food etc.) were excluded. (7) Had received an intravenous injection of 10 mg I (or KI), 15 weeks previously and had been fed milk with an increased content of iodine for the first four weeks of that period. (8) Pregnant, 8 months.

group. Because it has been claimed that the excretion of iodine is greater in regions in which goiter is infrequent than in those in which it is prevalent, the figures have been aranged in two sets of columns, based on these regions.

Cursory examination seems to indicate a difference in the excretion of iodine in the urine in goitrous and goiter-poor areas. However, there is a great deal of overlapping and there are some noteworthy exceptions.

Even v. Fellenberg, one of the foremost exponents of the "iodine-lack" hypothesis, found a low excretion in almost goiter-free Bad Hall, Austria.[10] On the other hand, Liek[11] and Lunde[16] found high excretions in goitrous areas. The former of these was erroneously listed as non-goitrous by Curtis, Puppel, Cole, and Mathews,[27] and the latter report was completely neglected. The uncertainty as to the proper classification of New Orleans is referred to in footnote 10 to the table.

Within each division, there is wide variation in the values reported by different investigators. To some extent, this must be ascribed to the lack of accuracy in the analyses. Not one investigator has reported really satisfactory recovery of *small* amounts of iodine, comparable to those found in the samples of urine being examined, when such were added to the urine. Even as recently as 1954, Stanbury *et al.*[29] admitted that the method used, while giving satisfactory recovery (94 per cent) by unstated amounts added to 1 ml of urine, gave only 68 per cent recovery when added to 8 ml of urine. These workers employed a sliding scale of corrections. (Actually, there were *no* controls on the method used for the determination of ordinary iodine (I^{127}). The figures given are for the recovery of added radioactive iodine (I^{131}).) Hercus, Edson, Kennedy and Purves,[13] having recovered only seven-eighths of unstated added amounts, increased their observed values by one-seventh to obtain those reported.*

Even within the same series, in which the same analyst used the same method, there were great differences. Naturally, these differences were greater the larger the number

* Letter from Dr. Purves.

TABLE III

Usual Daily Excretion of Iodine in the Urine of Adults (16 years or older)

Author	Non-goitrous regions						Goitrous regions						
				Iodine						Iodine			
	Place (1)	Persons	Urines	Min	Max	Av	Place (1)	Persons	Urines	Min	Max	Av	Footnotes*
		No.	No.	μg	μg	μg		No.	No.	μg	μg	μg	
v. Fellenberg[7]	Switzerland	7	7	28	108	64	Switzerland	18	18	4	29	19	(2)
v. Fellenberg[8]	Italy	6	6	30	140	79	—	—	—	—	—	—	(2)
v. Fellenberg[9]	Norway	8	8	94	240	146	—	—	—	—	—	—	(2)
v. Fellenberg[10]	Bad Hall	4	4	20	79	45	—	—	—	—	—	—	(2)
Liek[11]	—	—	—	—	—	—	Danzig	5	5	200	590	343	—
Hercus & Roberts[12]	—	—	—	—	—	—	N. Zealand	7	23	11	384	71	(3)
Hercus & others[13]	Australia	?	57	39	894	179	N. Zealand	?	155	10	914	58	—
	Samoa, etc.	?	18	55	232	162	—	—	—	—	—	—	—
Lunde[14]	—	—	—	—	—	—	Norway	54	64	6	237	63	(2)
Lunde[15]	—	—	—	—	—	—	Norway	?	23	132	245	?	—
McClendon[16]	—	—	—	—	—	—	Minn.	6	8	8	11	10	—
Bodnar & Straub[17]	—	—	—	—	—	—	Hungary	3	3	30	45	35	—
Scheringer[18]	Berlin	30	61	75	389	161	—	—	—	—	—	—	(4)
Kupzis[19]	Lithuania	5	5	63	157	118	Lithuania	3	3	62	106	83	—
Boe & Elmer[3]	Oslo	1	2	53	62	57	—	—	—	—	—	—	—
Jetta[20]	Netherlands	10	10	33	93	51	Netherlands	10	10	14	52	29	(5)
Jetta[20]	Netherlands	6	6	87	252	186	—	6	6	19	120	47	(2,6)
Schittenhelm & Eisler[21]	Kiel	1	15	16	41	28	—	—	—	—	—	—	(7A)
	—	1	15	17	33	23	—	—	—	—	—	—	(7B)
Elmer[22]	—	—	—	—	—	—	Poland	3	3	31	75	48	—
Elmer & Scheps[23]	—	—	—	—	—	—	Poland	2	2	34	40	36	(8)
Elmer[24]	—	—	—	—	—	—	Poland	?	?	20	70	?	—
Szasz[25]	Czech.	3	5	14	29	20	—	—	—	—	—	—	—
Moore[26]	(N. Orleans)	9	90	60	270	117	(N. Orleans)	9	90	60	270	117	(10)
Curtis & others[27]	—	—	—	—	—	—	Columbus	11	169	7	196	53	(11)
Stanbury & others[29]	—	—	—	—	—	—	Mendoza, Argentina	99	211?	?	460	28	(12) —

*Footnotes: (1) For complete identification of localities, consult original reports. (2) Based on night urines only. See Greenwald[30] for criticism of this practice. (3) Later repudiated by Hercus and Purves. Letter to I. Greenwald. (4) Six males, 11 non-pregnant and 13 pregnant women. (5) Analyses on composite urines of six days per person. (6) Analyses on composite of three night urines per person. (7) Same myxedematous patient: A. on vegetarian diet; B. on one containing meat. (8) 34 μg per day over a four-day period; 40 μg a day over a three-day period. (9) No definite statement as to the prevalence of goiter but, apparently, at a resort for the treatment of goiter. Data are from normal individuals. (10) Ten days' collection of urine from each patient, but it is not clear whether 90 urines or but 9 composites were analyzed. New Orleans classified as non-goitrous by Curtis and associates, but Mahorner and Barrow[28] had a very different opinion. (11) "Foods known to have a high iodine content, particularly seafood, were excluded" (p. 1015). (12) Euthyroid goitrous patients. Figures for the urinary iodine were not available but were approximated from the published charts. *"One patient . . . whose mean excretion was 1000 μg. per day was omitted from this graph."*

of persons or of urines examined. With 99 and 155 persons, the variations were 167 and 91 fold, respectively.

Probably some of these differences were due to carelessness in the collection of urine. Not one investigator reported that he had controlled the completeness of collection by determining the amount of urinary creatinine (or of total nitrogen, in those experiments in which the diet was supposed to be uniform). (See Greenwald[30] for more detailed criticisms of the adequacy of collection and of the methods of analysis.)

However, the greater part of the variations was probably due to fluctuations in the intake of iodine. This is of the greatest importance because of the great avidity of the thyroid for iodine and the length of time over which the thyroid may continue to store iodine.[2,13,21,24,29,31]

It is interesting to observe that, in the experiments reported by Puppel and Curtis[6] from Columbus, Ohio, a goitrous region, the subjects refrained from all seafood. Nevertheless, in none of the five consecutive periods of three days each, did the intake of subject G (Table II) fall below 449 μg, or 150 μg per day. This is almost as great as the average reported from any non-goitrous region and is greater than from most.

Of the eleven adults studied by Curtis and associates,[27] two collected urines for only three and four days, respectively. Of the remaining nine, who collected urines for eight days or more, seven excreted at least 104 μg on at least one day. Allowing for iodine in the feces and sweat and for the failure to excrete increased intakes of iodine promptly, it seems that most of the subjects must have ingested more than 200 μg of iodine occasionally, *even in this goitrous region, without the use of any seafood.*

Even in exceedingly goitrous Mendoza, Argentina[29] no fewer than 7 out of the 99 subjects had an average excretion, for two or three days, of over 150 μg of iodine per day, and one, deliberately excluded from consideration, had an average of 1000 μg. May not the other 92 have indulged in foods that induced an excretion as high as 150 μg, or more, at times other than the two or three days when they happened to be under investigation?

If the distribution found by Stanbury and associates[29] is to be regarded as indicating, not the amounts ingested by these 99 or 100 individuals throughout the year, but rather as the distribution of intakes by any given person throughout the year, it would appear that the inhabitants of Mendoza excrete over 150 μg of iodine on some 26 to 29 days in the year. From the data presented by Stanbury and associates (p. 62) it would appear that even with a daily intake of 500 μg of iodine for from 26–29 *consecutive* days, the excretion would not be more than 150 μg even on the last day.

Even on 1500 μg per day for 33 days, the three subjects excreted only 626, 386 or 307 μg, respectively, on the last day. It is true that these individuals had goiters and that normal glands might be saturated with iodine more readily. However, it is apparent that the excretion in the urine for even several consecutive days is not, necessarily, a good measure of the customary intake over a long period.

Other Factors

The effect of season upon the intake of iodine has been neglected by all except Hercus and Roberts[12] and their results were later repudiated by Hercus. Yet the character of food, particularly of vegetables and fruits, varies greatly through the year in all countries, even including our own with its great and varied territory and superior means of transportation. In other countries this effect is more marked.

Another influence that must be considered is the observance of Lent and similar meatless periods. At such times, in many countries, ocean fish, whether fresh, pickled, canned, or dried, are used to a considerable extent. Unless the period of observation includes such periods, it must give an erroneous impression of the amount of iodine ingested through the year.

To sum up: The available data for the excretion of iodine in the urine are unsatisfactory because of poor methods of analysis

and lack of control of qualitative collections of the urine. Even if these two were at all adequate, the great variation in excretion by any given individual over any appreciable time (8 to 35 days, sometimes only 3 or 4 days) indicates an even greater variation in consumption. Even the longest of these periods may not furnish a reliable index of the annual intake because of the great avidity of the thyroid for iodine and the long period over which a retention of iodine may occur.

For a criticism of the evidence purporting to show a difference in consumption based upon analyses of food and water see previous reviews.[30,32]

IV. Attempts to Produce Goiter in Animals by Diets Low in Iodine

In 1949, Curtis and Fertman[33] wrote: "Baumann and Roos and also Oswald were the first to observe that if iodine is withheld compensatory hypertrophy of the thyroid occurs."

There is nothing, however, about withholding iodine in either of the papers cited. Both state that the *concentration* of iodine in the thyroids from goitrous regions was less than in those from non-goitrous districts, but Oswald[34] emphasized that the *content* of iodine was greater in the normal thyroids from goitrous districts than in those from other places and that it was even greater in goiters than in normal glands.

Neither Baumann and Roos nor Oswald, nor anyone else, has yet produced goiter by simple withdrawal of iodine.

Large thyroids have been produced in animals upon diets made up of certain few natural foods, but to prevent such enlargement has required the addition to the diet of comparatively large quantities of iodine, and the thyroids of normal weight, when analyzed, contained much more than the normal amounts of iodine. Such diets must be considered to have contained positive goitrogens and the action of iodine regarded as pharmacodynamic.[30,32]

There have been six reports of experiments in which considerable quantities of purified food substances were used. In all, the protein was casein. Two of these reports[35,36] are of comparatively little significance because of the small number of animals and because a low concentration of iodine in the food was not established by analysis. At that, Jackson and P'An[35] found no differences between the volumes of the thyroids of rats that received added iodine and those of animals that did not.

Sampson and Korenchevsky[36] employed a diet deficient in vitamin A and containing heated casein, upon which three pairs of rats responded to the addition of 7.7 and 10 μg, respectively, of iodine per rat per day with thyroids that were slightly lighter, per 100 gm rat, than were those of litter-mates that did not receive such additions. However, pairs of their litter-mates upon a supposedly complete diet had thyroids that were only slightly lighter (2 sets) or considerably heavier (1 set). In all cases, the weights per 100 gm rat were considerably greater than is generally considered to be normal, indicating the presence of a goitrogenic agent. Possibly, this was the irradiated cottonseed-oil, which constituted 14 per cent of the diet.

By comparing only litter-mates of the same sex and at the same age and time on the diets, Coplan and Sampson[37] came to the conclusion that those rats that did not receive added iodine had slightly heavier thyroids than those that did, for a period of from 14 to 21 days for the males and up to 47 days for the females. Thereafter, they had lighter thyroids. Microscopical examination confirmed hypertrophy of the thyroids in the shorter periods and atrophy in the longer ones. However, the number of animals was small, the casein used for the control and experimental animals was not the same, all the thyroids weighed more than is now considered normal, and the amount of iodine added was large, about 1.6 mg per 4000 calories or about 16 μg per rat, per day. Again, the presence of a goitrogenic agent is indicated. Possibly, this was the large amount of carotene fed. With the same dosage of carotene, Sherwood and Luckner[38] observed changes in the histology of the glands. However, they did not weigh the thyroids.

In three sets of experiments, nearly all of

the constituents of the diets were purified substances. The largest number of animals were employed by Carpenter and Sharpless.[39] As Table IV shows, the experimental diet was inadequate, for the rats did not grow well.

TABLE IV

Weight and Iodine Content of Thyroids from Rats
Data of Carpenter and Sharpless[39]

The experimental diets contained 12% casein, 5% butter-fat, sucrose, vitamin supplements, and salt. There were 25 animals in each group.

Diet	Duration	Final body weight	Iodine intake per day	Thyroids per 100 gm rat	
				Weight	Iodine
	days	*gm*	*μg*	*mg*	*μg*
Stock	82	266	—	6.1	2.8
Stock	123	319	—	5.8	2.9
38B	82	118	<0.16	6.3	7.8
41	82	165	<0.15	5.3	5.3
41	123	169	<0.15	5.8	10.5
41 + 0.025% KI	82	144	1679	5.2	15.3
41 + 0.025% KI	123	167	1553	5.5	18.6

However, addition of iodine did not help matters. The uniformly small weight of the thyroids is noteworthy. Even more so is the high iodine content of the thyroids of the animals on the diets of very low iodine content.

The experiments of Van Middlesworth[40] have not been reported in detail, but he stated that he had kept rats in good condition and with small thyroids for 18 months on a diet containing from 20 to 30 μg of iodine per kilogram. Similar results were reported for mice by Axelrad and Leblond.[41]

It may be that casein contains particularly potent organic compounds of iodine.[42] If so, it is difficult to understand how goiter became so prevalent in The Netherlands and in Ohio, Michigan, and Wisconsin in the early years of this century, and in Switzerland and southern Bavaria at an earlier period.

It is highly desirable that these experiments should be repeated with other purified proteins, both of animal and vegetable origin.

The reports reviewed in this section show that diets of low iodine content but made up of purified constituents have not produced goiter in rats or mice. Enlarged thyroids have been produced by diets limited to certain foods, but to counteract these required comparatively large amounts of iodine and the accumulation of large amounts of iodine in the thyroids. These facts are believed to indicate the presence of goitrogenic agents in the foods and of a pharmacodynamic action of the iodine.

V. Evidence from the Use of Iodized Salt

Much has been made of the reduction in the incidence of goiter among school children and, in Switzerland, of neo-natal goiter also, that has followed the use of iodized salt.

Actually, the change in Switzerland is only the continuation of a process that has been going on for over a century.[43,44] The proportion of conscripts rejected because of goiter showed a greater fall between 1905 and 1910 than in any subsequent five-year period.[45,46]

Decreases such as those that have followed the introduction of iodized salt have been observed repeatedly, without benefit of iodine, not only in Switzerland, but in France,[47] North America,[48,49] Colombia,[50] Argentina,[51,52] and West Africa.[53]

It is interesting that, in these nearly fifty years of propaganda for iodine, there has been but one properly controlled experiment purporting to show that iodine has any value whatever in lessening the incidence of goiter in school children. In the much-quoted experiment of Marine and Kimball at Akron, Ohio,[54] the children were asked to volunteer for the administration of iodide. It is certainly hazardous to assume that all other conditions were the same in the two groups of a population so heterogeneous as that of Akron. It is not impossible, because of differences in dietary habits, that the children who did not volunteer may have had a higher intake of iodine, *for the year*, than those who received iodine in school. In the Swiss experiment,[55] the children were selected by the teacher for "practical reasons." We have not been told what these were. As in Akron, though probably to a lesser extent, there may have been differences in living conditions and in dietary habits.

The first, and only, properly controlled experiment was that of Scrimshaw, Cabezas,

Castillo, and Mendez.[56] Neither the children, nor their parents, nor the examiners knew which children had received the equivalent of 5 mg of iodine every week for from 14 to 28 weeks and which children had received placebos. The thyroids of those who received the iodine became smaller; those of the children who received placebos did not. However, 16 weeks after the cessation of these large doses, the thyroids had returned to their former size. Sixteen weeks is a remarkably short period for a deficiency disease to manifest itself after such a period of saturation, particularly since the foods were certainly not free from iodine. As a matter of fact, Cabezas, Pineda, and Scrimshaw[57] had previously reported that the native salt available in San Salvador contained an average of 22 parts of iodine per million. This is four times as much as has been credited with reducing the incidence of goiter in Switzerland[58] and in Poland.[59] The ingestion of but 5 gm of this native salt per day would provide some 110 μg of iodine. Since the food was certainly not free from iodine and since 5 gm of salt is a rather small amount, the intake of iodine by adults was probably well over 150 μg a day. As may be seen from Tables I, II, and III, this is about as much as was customarily excreted, or ingested, anywhere. Nevertheless, the incidence of goiter among the school children was 13 per cent for the country as a whole and 29 per cent in the rural districts.

With the use of salt that contains one part of iodine per 10,000, as is now recommended for San Salvador, the United States, and elsewhere, 5 gm of salt would furnish 500 μg of iodine, which exceeds the customary intake anywhere in the world.

Dangers of Iodized Salt

The use of iodized salt is not without its dangers. The older literature contains many accounts of hyperthyroidism developing in *people with goiter,* after the administration of iodides. In 1931, Plummer[60] reported an epidemic of exophthalmic goiter that developed at the time that iodized salt was introduced. Stanbury and associates[29] observed one case of hyperthyroidism in a group of three patients who received 1500 μg of iodine daily for 33 days. This first became evident as a high concentration of protein-bound iodine in the blood in 14 days. After 78 days, classical hyperthyroidism was evident.

In New Zealand, the use of salt containing one part of potassium iodide in 20,000 has been credited with having produced a marked decrease in the incidence of goiter among school children.[61] However, the number of admissions to the hospitals because of thyroid disease, other than exophthalmic goiter, in the five years following the adoption of this salt (after a longer period with a lower concentration of iodine) fell very little. The number of patients admitted because of exophthalmic goiter increased by almost the same number: 232 vs. 276.

In Lausanne, Switzerland, the proportion of adenomas encountered in all the autopsies increased from 1936–37 to 1946, in all except the younger age groups, whether the comparison was between persons of either or both sexes at the same age or between groups dying in 1936–37 with similar groups dying ten years older in 1946.[62]

In 1932, attention was called* to the increase in the death rate from exophthalmic goiter among insured persons in the period 1922–1930, as compared with 1911–1920. Better diagnosis was considered a possible factor but not the sole cause. May not the introduction of iodized salt have been a factor?

Marine has lately (*Annals of Internal Medicine* 41: 875, 1954) recognized this increase in the incidence of hyperthyroidism. He regards it as a temporary phase which is diminishing as the number of new goiters decreases. His two authorities for this belief are more than twenty years old. Perhaps the number of new goiters has since continued to decrease and perhaps the incidence of thyrotoxicosis has similarly diminished, but there is no satisfactory evidence connecting either or both of these with the use of iodized salt.

In this section it has been shown that the decreases in the incidence of goiter that have

* *Statistical Bulletin of the Metropolitan Life Insurance Company,* vol. 13, no. 11, p. 8.

followed the use of iodized salt have been paralleled or exceeded many times and in many places without any known change in the intake of iodine, or any reason to suspect that there had been any. In the only properly controlled experiment, even large doses (5 mg of iodine a week for many weeks), failed to prevent the recurrence of the goiters within a few weeks after the administration of iodine was stopped. Examples of the possible ill-effects of the use of iodized salt have been given.

Summary

The literature relating to the iodine requirements of humans has been reviewed. It has been found that the analytical methods used were poor, that little care, if any, had been taken to insure quantitative correction of the excreta, and that the hourly excretion of iodine in the urine during the night had, without justification, been taken as the same as during the day. However, taking the data for what they may be worth, the variation in the urinary iodine in both goitrous and non-goitrous regions was tremendous, with so much overlapping that it is impossible to conclude that there is any consistent and regular difference between the two.

Apparently, equilibrium has been obtained quite frequently, with an intake no greater than from 50 to 75 μg of iodine per day. This amount has been exceeded frequently by the intake, or excretion, in goitrous regions, *even with total exclusion of all seafood.*

Experiments with diets of purified constituents showed that rats and mice could grow and have small thyroids with intakes of less than 15 μg of iodine per 3000 calories. This value (15 μg) is of the order of the excretion by fasting men.

The decreases in the incidence of goiter that have followed the introduction of iodized salt have been paralleled or exceeded many times and in many places without any known change in the intake of iodine or any reason to believe that there had been any.

Even if it be conceded that the use of iodized salt has been responsible for a reduction in the incidence of goiter, one may not regard the amount of iodine so furnished as the requirement. To do this would resemble the setting of the requirement for iron as the amount required to cure hypochromic anemia or as the amount required to prevent anemia in severe infestation with hookworm. It is worse, for the excess of iron is probably harmless and the excess of iodine frequently is not.

It would seem, therefore, that in spite of a large number of clinical and animal investigations, the human requirement for iodine has not been finally established.

However, it appears to be small, less than 100 μg per day, and there is no satisfactory evidence that the customary diet, anywhere in the world, does not furnish an adequate amount.

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The Effect of Supplements of Animal and Vegetable Protein, Vitamin B_{12}, and Aureomycin on Hematological Values in Central American School Children

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With the assistance of J. Antonio Muñoz, M.D. and Adela Cabezas, M.D.

Comparative studies of the effect of animal and vegetable protein-containing supplements on the health and development of school children have been few and of relatively short duration.[1-3] Investigations of the effect of vitamin B_{12} on the development of school children have been generally inconclusive,[4-8] while trials of antibiotics for this purpose have been reported only from this laboratory.[9,10]

The administration of supplements of animal protein, vegetable protein, vegetable protein plus vitamin B_{12}, and vitamin B_{12} alone in school children of El Salvador and Guatemala was begun in 1950. At the same time, vegetable protein plus Aureomycin® and Aureomycin alone were administered in Guatemala. The design of this experiment and the results of successive height and weight measurements are described in the initial report.[9] The children in El Salvador averaged more than one year behind those of the United States in height and weight and those in Guatemala more than two and one-half years behind.[11] Detailed hematologic observations were also considered necessary because of the lack of previous experience with the long continued administration of vitamin B_{12}, or small doses of Aureomycin, to essentially normal children. The present paper presents the hematological findings in this study.

Material and Methods

The subjects were in apparently good health, although heavily infested with parasites. *Ascaris lumbricoides* was found in 79 per cent of the children of El Salvador and in 84 per cent of the Guatemalans. *Trichuris trichiura* occurred in 9 per cent of the former and 36 per cent of the latter. *Necator americanus* was identified in the stools of 13 per cent in El Salvador but was not found in the group studied in Guatemala. All children were treated for intestinal parasites at the beginning of the study in El Salvador and during the first 2–3 months in Guatemala. The opportunities for reinfestation were so great that the antihelminthic did not decrease the incidence of infestation encountered at the beginning of the second year, although it may be presumed to have decreased the number of parasites.

The scheme of experimental treatment in the control groups and those receiving the food supplements are shown in Tables I and II,

* From the Institute of Nutrition of Central America and Panama (INCAP), Guatemala, Central America; with the cooperation of the Public Health Services of El Salvador and Guatemala.

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The blood samples were obtained with the help of Roberto Gándara, M.D., J. Antonio Muñoz, M.D., Ernesto Borjas, M.D., and Adela Cabezas, M.D.

TABLE I

Hematological Findings and Occurrence of Anemia among Treatment Groups in El Salvador

Locality	Treatment	Months Interval	Number 1st Exam.	Number 2nd Exam.	Red blood cells 1st Exam. Mean ± S.D.	Red blood cells 2nd Exam. Mean ± S.D.	Hemoglobin 1st Exam. Mean ± S.D.	Hemoglobin 2nd Exam. Mean ± S.D.	Hematocrit* 2nd Exam. Mean ± S.D.	Distribution of "anemia" and macrocytosis: % MCV >94	children anemic: Total No.	children anemic: No. MCV >94
					Millions per cu mm		*gm per 100 ml*		%			
					Urban							
Colombia	Animal protein lunch	5	50	30	4.45 0.52	4.37 0.39	12.3 1.0	11.5 1.2	39.9 2.5	26	11	4
Roosevelt	Control	5	50	37	4.18 0.60	4.49 0.24	11.6 0.5	11.2 1.0	38.9 2.6	2	16	1
					Rural							
Matazano	Control	3	22	15	4.21 0.45	4.27 0.38	11.6 1.2	11.0 1.6	37.1 3.9	6	6	1
Comecayo	Animal protein lunch	4	26	24	4.17 0.46	4.32 0.30	12.0 1.2	12.3 1.2	37.3 2.1	4	3	0
Portezuelo	Vegetable protein lunch	5	24	23	3.99 0.47	4.19 0.41	10.9 1.1	10.9 1.4	36.9 2.8	34	8	4
Portezuelo	Vegetable protein lunch + vit. B_{12} 20 μg.	5	26	26	3.86 0.35	4.35 0.32	10.9 1.4	11.5 1.1	37.6 2.4	42	7	4

* No hematocrit data available for first examination.

together with the presentation of the results. In one additional village in Guatemala, Xenacoj, some serial observations are mentioned in the text for 3 children receiving 20 μg of vitamin B_{12} and 2 receiving 50 mg of Aureomycin for 18 months. A larger number of children in these two Xenacoj groups are included in the tabulations in which each set of examinations is treated individually.

The initial diets were very low in both animal protein and vitamin A activity. Riboflavin and calcium also fell below the National Research Council (U.S.) recommendations.[12,13] The supplementary feeding improved the situation in regard to protein, riboflavin, and calcium, but still left the diets below the recommended intake of vitamin A.

In the morning as soon as possible after the children arrived at school, blood was drawn and placed in oxalated tubes prepared as suggested by Wintrobe.[14] The blood samples were kept under refrigeration from the time they were drawn and were usually examined the same day. In no case did more than 24 hours elapse before the examinations were completed. The standard instructions of Wintrobe[14] were used for the determinations of hematocrit and red blood cells. New International type B centrifuges, with tachometers, were employed in both Guatemala and the second examinations in El Salvador. Hemoglobin was determined by the method of Sahli, using a visual hemoglobinometer in El Salvador and a Klett photoelectric colorimeter in Guatemala.

Results

All of the mean values for children from El Salvador (Table I) and Guatemala (Table II) fell within the limits for United States children in this age range, and the standard deviations are not remarkable. The results of comparisons of values before and after the treatment administered to the groups in Xenacoj and those in Table I and II do not indicate a consistent advantage for any of the treatments employed.

The children in Xenacoj receiving vitamin B_{12} for 18 months and examined all four times had upon first examination an average red blood cell count of 4.05 millions per cu. mm., hemoglobin of 13.2 gm per 100 ml, and hemato-

TABLE II

Hematological Findings among Treatment Groups in Rural Guatemala

Locality	Treatment	No.	Red blood cells				Hemoglobin				Hematocrit			
			1st Exam. Mean ± S.D.	2nd Exam. Mean ± S.D.	3rd Exam. Mean ± S.D.	4th Exam. Mean ± S.D.	1st Exam. Mean ± S.D.	2nd Exam. Mean ± S.D.	3rd Exam. Mean ± S.D.	4th Exam. Mean ± S.D.	1st Exam. Mean ± S.D.	2nd Exam. Mean ± S.D.	3rd Exam. Mean ± S.D.	4th Exam. Mean ± S.D.
			Millions per cu mm				*gm per 100 ml*				%			
San Antonio	Control	20	4.38	4.55	4.48	4.32	12.8	12.3	13.5	13.9	41	42	42	42
			0.56	0.32	0.30	0.24	1.2	0.9	0.8	0.8	3.0	2.3	1.9	2.1
Santa Maria	Animal protein snack	26	4.47	4.50	4.58	4.50	13.4	13.0	13.0	14.3	42	42	43	44
			0.45	0.33	0.36	0.30	0.9	0.9	0.9	0.9	2.7	2.2	2.2	2.2
Magdalena	Vegetable protein snack	11	4.14	4.48	4.58	4.39	13.1	11.9	13.1	14.1	42	44	43	43
			0.70	0.22	0.56	0.33	1.1	—*	0.9	0.9	2.6	—*	1.8	2.0
Magdalena	Vegetable protein snack + vit. B_{12} 20 μg	11	4.42	4.68	4.36	4.54	13.5	12.0	13.2	14.5	42	43	42	43
			0.42	0.28	0.42	0.24	1.1	1.1	1.0	0.6	2.8	3.0	2.3	1.5
Magdalena	Vegetable protein snack + Aureomycin 50 mg	9	4.57	4.69	4.55	4.85	13.8	12.6	13.3	14.7	41	44	44	44
			0.51	0.41	0.37	0.39	0.7	—*	0.8	1.0	1.4	—*	2.0	1.5

All of the same children are represented on first, third, and fourth examinations. Due to local circumstances, fewer were included on the second examination. The second examination means marked with an asterisk (*) represent too few observations to justify a value for standard deviation. The interval between the first and second examinations was 5 months and between the second and third and the third and fourth was 6 months.

TABLE III

Occurrence of Anemia and Macrocytosis among Treatment Groups in Rural Guatemala

Locality	Treatment	1st Examination				2nd Examination				3rd Examination				4th Examination			
				Children "anemic"				Children "anemic"				Children "anemic"				Children "anemic"	
		Total No.	% MCV >94 $cu\ \mu$	No.	No. MCV >94 $cu\ \mu$	Total No.	% MCV >94 $cu\ \mu$	No.	No. MCV >94 $cu\ \mu$	Total No.	% MCV >94 $cu\ \mu$	No.	No. MCV >94 $cu\ \mu$	Total No.	% MCV >94 $cu\ \mu$	No.	No. MCV >94 $cu\ \mu$
San Antonio	Control	53	49	13	13	43	37	5	4	32	53	2	2	28	64	3	2
Santa Maria	Animal protein snack	61	50	5	5	56	53	4	4	32	47	1	1	30	67	3	2
Magdalena	Vegetable protein snack	30	73	14	13	12	50	0	—	12	50	2	2	14	57	3	3
Magdalena	Vegetable protein snack + vit. B_{12}	22	45	2	2	10	50	1	1	11	64	3	3	18	56	0	—
Magdalena	Vegetable protein snack + Aureomycin	24	66	7	7	9	66	0	—	12	67	2	2	13	23	0	—
Xenacoj	Vitamin B_{12}	18	55	3	2	13	46	4	4	8	25	1	1	6	83	0	—
Xenacoj	Aureomycin	20	40	0	—	18	61	6	5	7	57	0	—	7	71	1	1

The interval between the first and second examinations was 5 months, and between the second and third and the third and fourth was 6 months.

crit of 41 per cent. The two receiving Aureomycin for the same period had an average red blood cell count of 4.26 millions per cu. mm., hemoglobin 12.4 gm per 100 ml, and hematocrit of 41 per cent.

The percentage of children with mean corpuscular volume (M.C.V.) greater than 94 cu μ is given in Table III for Guatemala. The value of 94 cu μ was chosen because Wintrobe[14] has used this value as the lower limit in macrocytic anemia of adults. Since children tend to have smaller mean red cell values this figure should give a conservative estimate of the amount of macrocytosis. Of possibly greater interest in these tables is the distribution of M.C.V. values in children considered to have anemia. For the purpose of this tabulation, children with a red blood cell count of less than 4.1 million per cu mm, a hemoglobin of less than 10.6 gm per 100 ml, or a hematocrit of less than 32.5 per cent were arbitrarily classified as anemic. These figures are an estimated one standard deviation below the normal values for children from 6 to 10 years of age given by Wintrobe.[14] None of these children had a M.C.V. under 86 cu μ. On the other hand, 66 to 100 per cent had a M.C.V. over 94 cu μ.

Unfortunately, comparable values cannot be presented from El Salvador, since a suitable centrifuge was not available when the initial surveys were done. Upon the second examination, the percentage of cases with M.C.V. greater than 94 cu μ varied from less than 10 per cent in Comecayo, Matazano, and Roosevelt schools to 26 and 42 per cent, respectively, in the schools Colombia and Portezuelo. Although the relative number of children with anemia was greater in El Salvador than in Guatemala on this second examination, the incidence of macrocytosis was not as great. The incidence of anemia in the first examination in El Salvador varied from 28 to 91 per cent, a far greater percentage than in Guatemala.

Discussion

Initial Hematological Values

As stated above, the incidence of anemia in El Salvador, as based on the criteria cited, was relatively high. Low hemoglobin values were the most common basis for classifying these children as anemic. The average red blood cell counts were only slightly below those for the United States. Since the average hematocrit values were considerably higher, nearly all the anemia cases were macrocytic in type. No case of microcytosis was observed, even though hookworm infestation was common among the groups studied in El Salvador.

The poor quality of the protein in the diets and perhaps the deficiency of one or more vitamins of hematopoietic importance are believed to be responsible for the tendency to macrocytosis. It is of interest that, in general, the entire distribution about the mean of values for M.C.V. was shifted toward the macrocytic side.

Higher hemoglobin values were observed in Guatemala than in El Salvador. As a result of the higher hemoglobin values, the incidence of anemia tended to be less in Guatemala and to be due largely to low red cell values. There is no reason to believe that the altitude (6,000 feet) at which the Guatemalan children lived was sufficient to explain the increase.[15]

Effect of Treatment

The figures given in Table I show that the treatment had no striking effect on hematological values. Although statistically significant at the 5 per cent level, the slight improvement in red blood cell count in the urban control group in El Salvador and one of the vegetable protein groups in Guatemala is of little practical importance and was probably a reflection of seasonal factors. The seasonal drop observed in hemoglobin in the urban schools in El Salvador was unrelated to treatment.

Treatment differences in hematocrit could be tested only for the data obtained in Guatemala, but no effects on hematocrit values were observed. In Guatemala, where it was possible to evaluate the effect of the various treatments on the incidence of macrocytosis in children with anemia, no consistent change in the high percentage of macrocytosis was observed. It is of interest to note that the vegetable protein snacks offered in Magdalena

were apparently effective in reducing the percentage of children with anemia.

The group receiving vitamin B_{12} in addition to the vegetable protein containing lunch in El Salvador had a slightly lower initial mean red blood cell value. Although this had increased significantly to the values observed for the other rural groups upon re-examination five months later, no special significance is attached to this isolated finding.

Summary

Hematological studies were carried out in two urban and three rural schools in El Salvador and four rural schools in Guatemala. Initial values for 100 urban children in El Salvador were: red blood cells 4.31 (S.D. 0.57) millions per cu mm, hemoglobin 12.0 (S.D. 0.8) gm per 100 ml, and for 98 children from the rural schools, red blood cells 4.05 (S.D. 0.45) millions per cu mm, hemoglobin 11.4 (S.D. 1.3) gm per 100 ml. Corresponding values for 228 rural children in Guatemala were red blood cells 4.40 (S.D. 0.42) millions per cu mm, hemoglobin 13.3 (S.D. 1.0) gm per 100 ml, and hematocrit 42.0 (S.D. 2.5) per cent. In Guatemala, 49 per cent of the children had mean corpuscular volumes greater than 94 cu μ. Only 19 per cent had hemoglobin values less than 10.6 per 100 ml or red blood cell counts less than 4.1 millions per cu mm.

The children in an urban school in El Salvador were given an excellent lunch rich in animal protein without producing any change in five months compared with those in an urban control school. Vegetable and animal protein lunches, respectively, and a vegetable protein lunch plus 20 μg of oral vitamin B_{12} daily had no effect on red blood cell count or hemoglobin values during five months in El Salvador or two years in Guatemala, compared with rural control schools in each country. The daily oral administration of 20 μg of vitamin B_{12} or 50 mg of Aureomycin to rural Guatemalan school children in addition to a vegetable protein lunch, as well as the provision of 50 mg of Aureomycin or 20 μg of vitamin B_{12} alone, had no significant effect on blood values during a two-year period.

Acknowledgment

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Lack of Effect of a High Fat Intake on Serum Lipid Levels

By GEORGE V. MANN, SC.D., M.D.*

THE EVIDENCE indicates that the cholesterol intake of human subjects when within the limits of conventional intake, does not appreciably influence the serum lipids.[1,2] The dietary levels of total fat and total calories appear to be more pertinent to this problem. Many studies have revealed that a reduction of dietary fat will often reduce the serum level of cholesterol, especially if this is originally elevated.[3] We have shown that limitation of calories inducing weight loss will reduce serum lipids if these are initially elevated.[4] Conversely, we showed that a caloric plethora, even in the absence of fat, would increase the cholesterol and lipoprotein levels of young adult subjects.[4] The corollary to the latter experiment is that of increasing the total fat intake while maintaining the caloric intake at a constant level. This experiment has been done in two young males using Pemmican as the principle source of food.

METHODS

The subjects were two healthy young males, "G" age 29 and "B" age 25 years, with initial relative weights of 0.96 and 1.15, respectively. These subjects were in weight equilibrium and were accustomed to diets supplying approximately 105 and 120 gm of fat daily, as estimated by a recall type of diet history.

The experimental diet plan is shown in Table I, with the gross composition as determined by calculation using standard food tables. The subjects were instructed to vary *only* the Pemmican* content of this diet in order to maintain their weights at the starting level. Subject B found this diet as outlined almost precisely sufficient, and subject G needed to make only a minor and temporary increase. Neither subject lost more than two pounds during the experiment.

Two control samples of venous blood were obtained from each subject at a three- or four-day interval before commencing the diet. The subjects were then instructed to begin the experimental diet and successive blood samples were taken on days 2, 4, 7, 11, and 15 thereafter. The subjects were then returned to their conventional diet and were bled again several weeks later.

The blood serum obtained was analyzed for total cholesterol by the method of Abell *et al.*[5] and for lipoproteins of the S_f 0–12, 12–20, 21–35, and 35–100 classes by the method of Gofman *et al.*[6]

RESULTS AND DISCUSSION

The serum data obtained are plotted for the two subjects in Figures 1 and 2. The S_f 0–11 class of lipoprotein showed no change and was not plotted.

Because there was but little evidence of trends of these data, the mean levels of the five observations during the Pemmican treat-

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* Supplied by Dr. Harry Spector, Chief, Quartermaster Food and Container Institute for the Armed Forces, Chicago Quartermaster Depot.

TABLE I

The Daily Food Intake of Two Experimental Subjects

Food	Amount	Fat	Protein	Carbohydrate	Calories
Pemmican	300 gm	141	150	—	1869
Fruit					
oranges	3	—	—	50	200
Soda crackers	8 (50 gm)	5	4	36	205
Milk	500 ml	20	18	25	352
Total gm		166	172	111	
Total cal		1494	688	444	2626
Per cent of total cal		57	26	17	100

ment were compared with the mean control (two observations) levels by the application of "t" tests. These procedures revealed no evidence that subject B had influenced his serum lipid levels by this high fat intake. The cholesterol and S_f 12–20 levels of subject G indicated only suggestive evidence ($0.10 > p > 0.05$) that they had been increased by the treatment. We interpret this to mean that under the conditions of this study the fat content of the diet was not a critical factor in controlling serum lipid levels.

The increase of the proportion of fat calories from about 40 per cent of the total to 57 per cent of the total was the limit of physiological tolerance of these subjects. Previous attempts of subject G to consume Pemmican solely were repeatedly unsuccessful. These

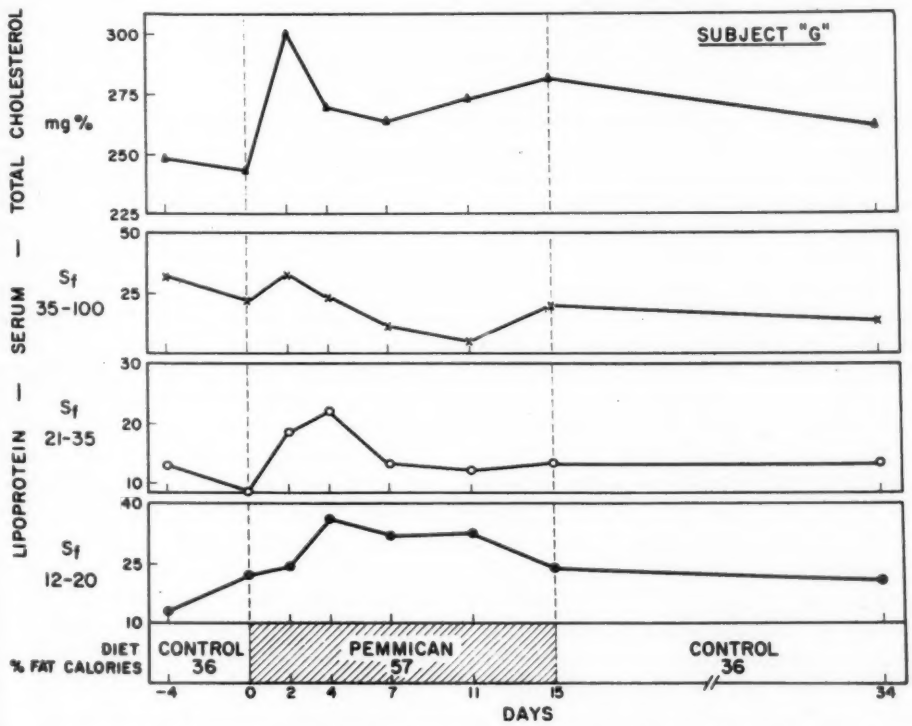

Fig. 1. The serum cholesterol and beta-lipoprotein levels in a young male subject maintained in weight balance for two weeks on a Pemmican diet supplying 57 per cent of the total calories as fat.

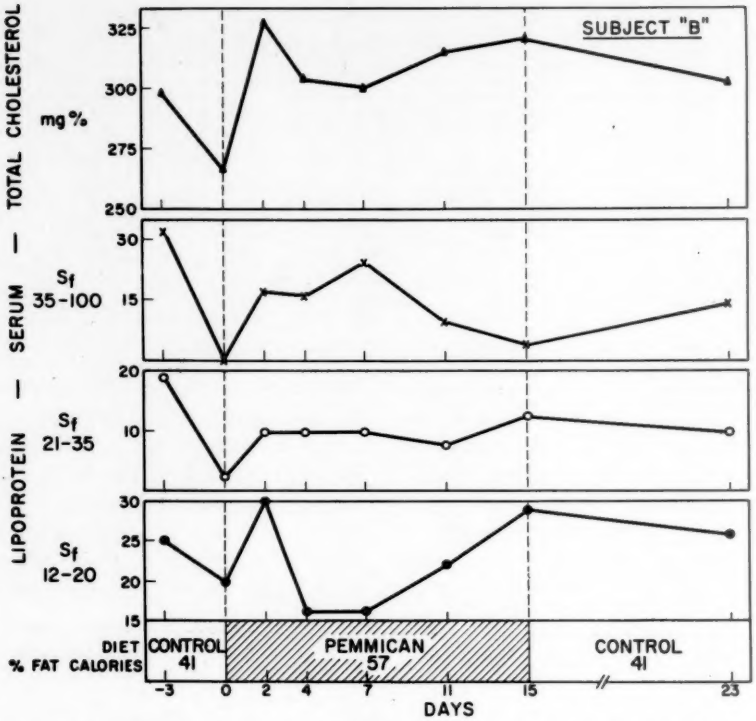

Fig. 2. The effects of a high fat diet composed largely of Pemmican on the serum lipids of a normal young male.

attempts failed because of anorexia and weakness and were associated with ketonuria and dehydration. The subject was engaged in a sedentary occupation requiring between 2500–3000 calories per day. He was strongly motivated by personal convictions in these dietary trials. This experience with high fat oral diets conforms with that of Kark *et al.*[7] and Consolazio *et al.*[8] There appears to be an upper limit of tolerance of fat in the metabolic mixture supplied by the diet.

In 1949, Sinclair *et al.*[9] reported studies on serum lipids in 161 Eskimos, and they have since supplemented this material with dietary evaluations and feeding experiments.[10] It should be emphasized that Brown doubts the validity of measurements of Eskimos' food consumption, and, in view of his experience with this problem and the complexities which have been introduced into the cultural characteristics of Eskimos by the opening of the North to white men, this skepticism deserves attention. Brown found that the cholesterol levels of adult Eskimos consuming a diet which was estimated to contribute 75 per cent of the calories as fat were lower than would be found in United States adults. Four of these Eskimos who by preliminary measurements were found to be consuming a diet with 55 per cent of fat calories were fed a Pemmican diet which supplied 75 per cent of calories as fat. During a six-day trial, the cholesterol, total fatty acid, and phospholipid content of the subjects' blood sera appeared to be increased. Those findings suggested to us that it would be difficult to establish that the increases observed were greater than could be attributed to random fluctuation. It will also be important to learn whether the body weights of these subjects were changed during the trials, for that factor will influence the serum cholesterol levels. Brown's data, as well as those presented here, suggest that there is an influence of the Pemmican diet upon the serum

cholesterol level especially, but that the increase demonstrated is too small to be irrefutable. More extensive studies of this phenomenon are indicated.

Summary

Two young men did not show a significant increase of serum cholesterol or various beta-lipoprotein fractions during 15 days on a diet of which 57 per cent of the calories came from fat as provided in Pemmican.

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Possible Sources of Proteins for Child Feeding in Underdeveloped Countries*

By M. AUTRET, PHARM. D. AND A. G. VAN VEEN, PH.D.

IT IS recognized nowadays that protein malnutrition in vulnerable groups, and especially in infants (after weaning) and in young children, is a worldwide problem. It is also recognized that the ideal solution of this problem would be a generous milk supply to all infants and children, but we are also quite aware that this ideal solution is not a practicable one, at least not in many underdeveloped countries, especially in the tropics. The efforts to find other solutions, that is, to find other suitable, protein-rich foods (or combinations) to prevent (and cure) protein malnutrition are of relatively recent date; to our regret they often lack the scientific background that would be desirable. It appears often to be difficult in many economically underdeveloped countries to develop research programs, which could give this scientific basis. This will be apparent in this lecture, in which a few projects will be discussed with which FAO is rather intimately concerned.

Two years ago a paper[1] was presented to the Second Conference of the International Union of Nutritional Sciences on the research problems concerned with local foods of special value for supplementary child feeding schemes. In this paper it was explained why it would be important to use locally produced protein-rich foods (or food combinations) other than milk in feeding schemes in many countries where insufficient milk can be produced or imported to satisfy the nutritional needs of infants, children, pregnant and nursing mothers, etc. Even the huge milk surpluses in a number of dairy countries at the present time do not solve the problem. Moreover, for older infants and young children, other protein foods besides milk are needed. In economically underdeveloped countries, those protein-rich foods have to be very cheap, and if they have to be processed for making them more suitable for transportation, storage, and distribution, the processing has also to be very cheap, and, therefore, relatively simple.

In the paper quoted a number of possibilities were mentioned, and the importance of more basic and applied research in this important field was stressed.

In the meantime, an excellent report has been published by the Medical Research Council[2] in which Dean reports on his experience in Germany after the war with certain cereal and soy mixtures in groups of children. Moreover, he discusses in this report the possible uses of plant proteins in child feeding, their advantage, disadvantages, and problems connected therewith.

In the present paper, attention is drawn to a few projects which are under way, and to promising products which FAO workers have been instrumental in developing. These do not, however, relate exclusively to vegetable proteins, but also to mixtures, and in one case even to a pure animal product.

This kind of food has drawn much attention all over the world, because only recently nutritionists have become aware of the fact that protein malnutrition in infants and young children is prevalent in many underdeveloped countries. In 1952, a FAO/WHO Conference in the Gambia, Africa, discussed protein malnutrition, and ways and means of preventing it. In 1953, two Regional Conferences were

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held, one in Indonesia for South and East Asia, and the other in Venezuela for Latin America. At both meetings, protein malnutrition and "local foods" formed the main items of the agenda. At the end of 1953, a joint FAO/WHO/Macy Foundation meeting in Jamaica discussed the same problem.[3] These meetings have done much to focus attention on protein malnutrition and the great need of suitable protein-rich foods for appropriate feeding of infants and young children.

Two remarks will have to be made here. One is, that the products to be described are not meant to replace milk* (as the main food for infants, for example), but are either to be used together with milk (if available) or as a source of good protein (and eventually other nutrients) for vulnerable groups if milk is not available. The second remark is concerned with the fact that although mainly processed foods will be mentioned here, this paper does not intend that they should not be consumed fresh. However, to make valuable food (or food-mixtures) more popular, especially in economically underdeveloped countries, the introduction by way of some sort of feeding scheme (for example, school feed) is to be recommended, and for this purpose they usually have to be processed. And this is also necessary if the foods concerned are only produced in certain seasons or in limited areas.

Soy Products

One of the projects FAO has been associated with for a long time is the so-called "soy milk" project in Indonesia. Soybeans form an important agricultural product in Indonesia; the population consumes them in different forms, mostly not suitable for child and infant feeding, and of low keeping quality. There is some dairy industry in a few parts of Indonesia, but this will probably never become sufficiently important to be able to supply cheap milk to all the members of the population who need it.

Before the War, experiments had been done with the product usually wrongly called soy milk, which had, however, certain drawbacks in connection with acceptability and nutritive value.[4] After the War, it was found in India that a much more acceptable product (from the point of view of taste, flavor, consistency) could be manufactured by adding some groundnut milk (which, incidentally, the Chinese knew for a long time) and, if available, malt. Experiments in orphanages and hospitals in Indonesia and elsewhere had shown, moreover, that the product was well tolerated.

The idea of using soy milk is, of course, not new. There are small, private soy milk factories in Hongkong and Manila, and in Mount Vernon, Ohio there is a factory which produces soy milk powder (and other soy protein products) for infants and children who are allergic to milk.

Through the FAO Technical Assistance program, it was possible to give help and encouragement to the Nutrition Institute in Djakarta for developing this project. First the product, called "saridele" (to avoid the word "milk") was produced on a small scale in the Institute and, according to information received, it appeared to be acceptable and digestible for infants and children, with the exception of certain cases where the "saridele" had not been heated sufficiently and digestive troubles were the result. Much to our regret, detailed reports have never been received on these feeding experiments.

The authorities were satisfied with the results and after the project had been thoroughly discussed in the National Nutrition Council in Indonesia, the Government requested UNICEF and FAO to assist it in setting up a "saridele" plant for the manufacture of this product for mother and child welfare centers and hospitals.

Probably it will be asked why the Government does not encourage the local manufacture in villages and households instead of concentrating on centralized manufacture of the product. The reply is that whereas in many villages "soy milk" is not unknown, "saridele"

* We would like to avoid the expression "milk substitute" to which many people object, because there is no natural food which can replace milk fully as far as nutritive value, digestibility, and suitability for infants are concerned. For this reason, we prefer the somewhat cumbersome term "(locally produced) protein-rich foods other than milk."

from soybean and groundnut certainly is. Introducing a new, hardly known food or food mixture in a country like Indonesia is a difficult and slow process; demonstration through feeding schemes is one of the best ways. Processing on a village scale or locally for hospitals, etc. would certainly lead to numerous difficulties, such as unhygienic manufacture and distribution, lack of suitable containers, and adulteration of the product with water, etc.

A product manufactured under hygienic conditions in a well-supervised plant, carefully standardized as to composition and packaging was, therefore, the choice of the Government.

One difficulty with packaging and distribution of liquid products in a country such as Indonesia, without important glass industries, and where tin cans usually make the product too expensive, is the container problem. Glass bottles are expensive, breakage is considerable, and their return to the factory not secure. It could, however, be shown that under the prevailing conditions, it would be cheaper to have the "saridele" spray-dried (which, of course, requires a higher initial capital investment) and packed in moisture-proof polythene bags, as is done nowadays with dried skim milk in tropical countries. This solved the problem.

As with all products which have to be "reconstituted" with water, there is always the danger of the reconstitution being done under unhygienic conditions, and the reconstituted product kept for too long a time. However, this is a general problem for all foods which are stored under more or less unhygienic conditions in tropical countries. And in hospitals and mother and child welfare centers, this danger can be easily eliminated.

The total capital investment of the Government and UNICEF (who will supply the plant) is about 6 or 7 million Rupiahs (about $700,000); the plant will produce at least 300 tons of the dry product a year.

Another well-known soybean product from Indonesia, *tempeh*, prepared by treating the cooked soybeans with a certain fungus, has drawn the attention of workers in Southern Rhodesia where soybeans are cultivated, but the local population is not much interested in consuming them. Tempeh has a high nutritive value and is highly digestible,[5] but the manufacture is somewhat difficult to control when the product is manufactured under simple conditions. This and other considerations were the basis in Indonesia of the conclusion that soy milk would be preferred to tempeh in the manufacture of a soy product for infants, and children.

FAO has been giving technical advice on the manufacture of tempeh in Southern Rhodesia, and it seems that the results of the large-scale experiments are very promising. It is to be hoped that these will be published, not only in connection with acceptability, but also concerning the technical problems, data on production costs, and so on.

In 1952 Dr. Dean published an important article[6] on the successful treatment of a number (about 20) of small children in Uganda suffering from kwashiorkor with an emulsified mixture of whole soybeans, bananas, and added vitamins. Sometimes maize flour was added, sometimes the soybeans substituted by dehydrated soy milk. These experiments proved that the soybean-banana combination was an excellent one, but it will be realized that this "enriched" mixture can only be prepared satisfactorily in well controlled institutes, hospitals, etc.

Peanut Presscake Flour

Vegetable protein-rich foods suitable for human consumption have been thoroughly reviewed by Dean.[6] The question is not to reconsider the whole subject, but we feel that more emphasis should be laid on the use of oil presscakes, by-products of the oil industry, which are such a valuable source of proteins of low cost. Studies of these presscakes have been made and interesting monographs on the subject are now available. Currently, FAO is paying more and more attention to the processing by industrial concerns, especially in Africa, of a presscake (the protein of which would not be damaged during the processing) which could provide, through sifting, a flour acceptable to children. The best would be to be able to produce on African markets an oil-extracted flour, of good keeping quality, of

good nutritive value, which could be used like peanut or baobab flours in the preparation of the "sauce africaine," which is in itself a complicated dish served with the basic food, the latter being always a starchy food: millet, maize, rice, or manioc. At the same time, we should aim at educating the mothers with a view to making them use this flour directly in the preparation of the millet, maize, or manioc paps which they give to their children. Various experiments have been performed; for example, a peanut "milk" has been given to children 4–6 months old who have previously been receiving only breast-milk and whose growth curves were no longer satisfactory; dried biscuits prepared with maize flour to which 40 per cent of peanut presscake flour have been added have also been tried. One of the industries in Nigeria is preparing a slightly roasted sifted flour which, either salted or sweetened, is well accepted. A very fine flour is obtained from the processing below 100° of an ordinary presscake which has undergone sifting through a special process; it is free of cellulose and silica and should be suitable for human consumption. Experiments on the nutritive value of the product, its digestibility and biological value, are at present under consideration, as well as experiments on young children and on adults by incorporating this product in various foods. Several firms in Nigeria and French West Africa are now actively engaged in the processing of products suitable for human consumption. Without having the same supplemental value as certain other protein sources, the peanut presscakes would certainly largely contribute to the improvement of the diet in underdeveloped regions. The cost of this product is at present 8 cents (U.S.) a kilogram.

Pulses and Fermented Milk Combinations

WHO and FAO have also been interested in infant and child feeding problems in the Near East, especially in connection with the Arab refugees, with whose nutrition problems both organizations are concerned. In cooperation with the Medical staff of UNWRA, it was found that combinations of *burghul* (parboiled wheat) chick-pea paste (*hommos*) and *leben* (sour milk) could substitute exensive infants' foods such as Pablum.® Burghul is an interesting analogue of parboiled rice. It is known from Turkey to Egypt and Iraq, and often used as a substitute for rice. For infant feeding it has to be pounded or ground into a fine powder. Chickpeas form a favorite dish in the Near East, often in the form of a paste with or without olive oil. Milk is not often consumed as such, but is usually converted, after boiling, into leben, which is more or less the equivalent of yoghurt in Turkey. Even the skim milk powder supplied by UNICEF and UNRWA in the Near East is usually, after reconstitution, converted into leben.

One of the most important things, of course, is to teach mothers and families that for infant feeding the burghul should not be too coarse and the leben not too sour.

One will ask why burghul is advocated and not wheat flour. The wheat varieties and wheat flours in the Near East are not standardized and, therefore, it is preferable to advocate a whole wheat product instead of wheat flour, in which ease the mothers probably would prefer a white, low-extraction flour. As to nutritive value, one can compare burghul with parboiled rice. Moreover, one gets the impression that burghul is preferred to ordinary wheat flour as a food.

W. H. Adolph, who had done such splendid work on the biochemistry of nutrition in China before the last War, during his stay at the American University of Beirut was interested in the same problems and co-operated with FAO; he found that the cooked chickpeas (hommos) and the burghul-hommos mixture both rank high in nutritive value with respect to the protein. This also held for "falafil," a chickpea-broadbean-burghul and "kishk," a mixture of burghul and leben (dried). The protein efficiency ratios of these products were much higher than other protein combinations used in the area. These interesting findings will be published shortly.

In the spring and summer when there is a (very relative) abundance of milk, the leben is dried together with burghul and pounded into a coarse powder which can be stored easily and is consumed during the next winter.

It can be reconstituted easily with hot water or milk, and remains of buttermilk. This "kishk" has also been tried by the UNRWA workers for infant feeding with good results. It is interesting to note that a product analogous to kishk is known in Turkey, where some sort of sour dough is made out of high-extraction wheat flour, which is dried in the shade after mixing with yoghurt and sometimes tomato paste and spices. The resulting product, "tarkana," can be kept for long periods of time and easily reconstituted with water to some sort of soup or porridge.

Fish Flour

Another product to which FAO has drawn the attention of nutritionists, biochemists, and governmental authorities is edible fish flour containing up to 75–80 per cent protein of high quality, as well as calcium and vitamin B_{12}. For the purpose of child and infant feeding, a cheap fish meal seemed to offer great advantages in connection with price, storage, etc. in comparison to canned fish or the dried and salted product. From the beginning, it was realized that in a number of countries a flavorless fish flour would be preferred, whereas in a number of other countries, such as in South East Asia and Africa, fish flour with certain flavors might be preferred.

During 1953, experiments were initiated with an edible fish flour which was developed by the Marine Oil Refiners of South Africa Limited. It was decided that Chile was a suitable place for initiating such experiments, in order to gain experience with the acceptability of such flours in local dishes and other food preparations. The reasons why Chile was chosen were these: (1) Chile has large fisheries resources which are only partly exploited; (2) the "fish consciousness" of the population and authorities of Chile is very high after the work of an FAO Technical Assistance Expert in Fisheries Propaganda, and of others; (3) the FAO Regional Office in Santiago has the services of a Nutrition and of a Fisheries Officer; (4) at present, the Chilean diet is short in animal protein; (5) official authorities, interested nutritionists, and other workers are eager to give their full cooperation.

In preparatory experiments, the fish flour was mixed into a number of foods such as vegetable soup, potato soup, tagliarini (alimentary paste), cochayuyo (edible algae), fried potatoes and lettuce, beet leaves pie, beans, beef stew, boiled potatoes, cocktail crackers, coffee cake, and white bread.

In the preliminary tests, these combinations were judged by a limited number of persons, who found the preparations generally acceptable except for the tagliarini, the cochayuyo, and the beef stew, about which the main complaint was that the texture was not normal (this may be overcome by using a finer milled fish flour). The beet leaves pie, the crackers (25 per cent fish flour), the coffee cake (10 per cent fish flour) and the bread (10 per cent fish flour) were unanimously accepted.

Based on these preliminary results, a large-scale trial was started involving 140 school children, 5 to 14 years old, who every day during six weeks, as part of their school lunch, each received an 80-gram bread roll made at a commercial bakery, which used flour containing 10 per cent of fish flour. Compared with normal bread, the only difference was a slightly darker color, the smell and taste, and form and consistency of crust and crumb being normal.

The bread was very well accepted by the children. There was not a single case of rejection or complaint. No digestive trouble traceable to the bread occurred.

Each bread roll contained 6.1 gm fish flour, which provided a child with a daily supplement of: 4.4 gm protein, 335 mg calcium, 329 mg phosphorus, and 3 mg iron, where the roll itself supplies 6.5 gm protein.

The same type of fish-flour-fortified flour was used during a short period in bread given to young men in a military camp. Here also, this type of bread was very well accepted.

After these results had been obtained, the Chilean Government sent a request to UNICEF and FAO to help them in setting up a plant for the manufacture of edible fish flour to be used mainly in supplementary feeding schemes.

In the meantime, a great number of nutritionists and government officials all over the world became interested in the great possi-

bilities of edible fish flour, and UNICEF and FAO are arranging for a series of acceptability tests in different countries in co-operation with local fisheries and nutrition experts. In Malaya, Indonesia, and the Philippines, a number of government workers have embarked on these experiments themselves. It is interesting to note that adults in Indonesia preferred a local fish flour of selar (Caranx spp.) with a rather pronounced flavor to a flavorless fish flour. According to information received, small children and infants do not show this preference, however.

In Africa, several experiments are in process and interesting results have already been reported. Apart from the Union of South Africa, which we have already mentioned, large quantities of fish meal are prepared for animal feeding, for example in Angola. The West Coast of Africa also offers very interesting fish potentialities, from Morocco to Angola. Some rivers such as the Niger, Ogoué, Chari, Lagone, and the lakes of Central and East Africa are also rich. Some fish flour suitable for human consumption has been experimentally produced on a pilot scale in the Gold Coast, and the product well accepted by the population. It is worth mentioning that the Gold Coast fish flour has excellent keeping qualities, in spite of its rather high fat content, and the reason for this is a matter worth investigation.

Again the "Service de l'Elévage et des productions animales" of French West Africa is considering the possibility of setting up a pilot plant in Dakar, while a private firm is willing to build a large plant for fish flour preparation in the same place.

In Uganda, the Animal Health Research laboratory has completed the laboratory research work. A pilot plant is being requested by the Uganda Fish Marketing Corporation.

Some experiments on the acceptability of various products have been carried out with fish products supplied by FAO. In Senegal and Haute-Volta, the Nutrition Mission in French West Africa, directed by Dr. A. Raoult, and in Cameroons the Nutrition Section of IRCAM, under Dr. R. Masseyeff, have used a fish autolysate prepared mainly out of fresh sardine offals. Dr. Raoult has distributed the autolysate in the form of a paste or of a dry product, to children over two years old. In some instances the product was also introduced in the diet of patients recovering from kwashiorkor. The product was very well accepted, and the results on the health and growth curves of the children will soon be available. However, it can already be stated that the influence was most favorable. Dr. Masseyeff[7] carried out tests of a different kind, i.e. acceptability tests as far as taste and flavor were concerned, among various tribes, and food dishes in the Cameroons. The excellent results achieved have been published: 87.5 per cent of the 4,500 people who have tried the product accepted it quite readily and often with enthusiasm. Only one Moslem tribe in Northern Cameroons refused to try the product.

Again, experiments on infants have been carried out in Dakar under careful medical control. The fish flour used in the tests was prepared from fresh fish fillets under hygienic conditions. The fat content varied from 3 to 8 per cent, according to the fish, and the process used. The quantity given daily varied from 10 to 50 gm. The preliminary results show that fish flour can be given to very young children, as early as three or four months of age; that is, as early as mixed feeding starts, provided the fat content is not higher than 3 per cent. When the fat content reaches 5 per cent, the fish flour is still well tolerated by infants of more than six months old. Fish flour with more fat—7–8 per cent content—was still acceptable to children between one and two years old.

Other experiments with both a tasteless and flavorless South African fish flour and a fish product from Iceland with fish taste and flavor, are now under way in Dakar, Brazzaville, and Leopoldville.

Again, for easier distribution, a biscuit mainly made of maize and fish flour is being prepared in Leopoldville.

In Uganda, three fish meals prepared by the Animal Nutrition Research Centre were tried by Dr. Welbourn as supplementary foods for mothers and children and were accepted

in various quantities by the majority of them. These fish meals were also tried by Dr. Trowell among sick children who had difficulty in digesting, and also among healthy children. The meal was added to soup and sauces to which it gave a pleasant taste, making them more appetizing.

mine digestibility and biological value. However, when discussing "supplementary biological values," information on the approximate content of essential amino acids may be helpful.

In Table I, we have given the essential amino acid contents of whole wheat, dry skim

TABLE I

Protein and Amino Acid Composition of Some Foodstuffs

	Calories	Protein	Arginine	Histidine	Isoleucine	Leucine	Lysine	Methionine Methionine	Phenylalanine	Threonine	Valine	Tryptophan	Tyrosine	Cystine
		gm	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*	*gm*
Wheat, whole, soft, 100 gm	333	10.5	0.48	0.24	0.45	0.79	0.30	0.28	0.57	0.37	0.48	0.14	0.45	0.20
Dry skim milk, 35 gm	126	12.6	0.52	0.32	0.92	1.36	1.07	0.39	0.68	0.58	0.86	0.18	0.74	0.12
Pulses, 50 gm	172	11.1	0.78	0.24	0.61	0.78	0.72	0.11–0.33	0.56	0.43	0.61	0.09	0.31	0.14
Fish meal, 15 gm	55	11	0.91	0.29	0.66	1.02	1.07	0.29	0.49	0.57	0.72	0.09	0.28	0.20

Sources: Calories and Protein: *FAO Food Composition Tables for international use*, 1949 and 1954. Amino Acies: Block and Bolling: *The Amino Acid Content of Protein and Foods*, 1951 (except fish meal). Amino Acids in Fish Meal: Deas, Ney, Tarr: Amino acids in fishery products, II. *Progress Reports of the Pacific Coast Stations*, Fish. Res. Board of Canada, Dece nber 1948, p. 97.

In encouraging and assisting such experiments, FAO and UNICEF have in mind that whereas for preliminary tests fish flour has to be imported, the ultimate aim is that the countries concerned produce the fish flour themselves. Probably only a few countries will be interested in continuing to import fish flour for large-scale feeding purposes.

In the meantime, two other fish flour producers have supplied us with samples of reasonably flavorless fish flours. The selling prices probably range between 10 and 25 cents (U.S.) per kilogram, which compares favorably with normal selling prices of skim milk powder.

Amino Acid Considerations

It will be useful to see whether a few of the findings mentioned above can be substantiated by calculations in connection with amino acid contents of proteins of such products as skim milk, fish flour, and pulses. We have to realize that such calculations have a *very relative value only*. Fish flours and pulse varieties do not have a constant composition. The knowledge of the amino acid contents of a certain protein does not enable us to determine digestibility and biological value. However, when discussing "supplementary biological values," information on the approximate content of essential amino acids may be helpful.

In Table I, we have given the essential amino acid contents of whole wheat, dry skim milk, pulses, and fish flour. For purposes of comparison, we calculated the amounts of essential amino acids in 35 gm of dry skim milk (usually 40 gm are used in UNICEF feeding programs), 50 gm pulses, and 15 gm fish meal, representing 12.5, 12.5, and 11 gm of protein.

We have compared, in Table III, the amounts of essential amino acids supplied by each of these "protective foods" (in the quantities indicated) in combination with 100 gm of whole wheat flour (because cereals often take the most prominent place in the diet of weaned infants) with the requirements of an infant of 6 kg as given in Table II. Such an infant would be about six months old in America or Europe, if it were well fed. In many underdeveloped countries, however, infants of 6 kg can be anywhere between six and ten months of age and generally will be still breast-fed, while receiving some other foods.

The same has been done for a 10-kg infant (which in many underdeveloped countries can have an age between one and two years and still be receiving some milk from the breast), increasing the amount of wheat flour from 100 to 200 gm (see Table IV). Of course, wheat can be substituted by rice (Table V) or

TABLE II

Infants' Requirements for Calories, Protein, and Amino Acids

	Calories	Protein	Argi-nine	Histi-dine	Isoleucine	Leucine	Lysine	Methio-nine	Phenyl-alanine	Threo-nine	Valine	Trypto-phan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Infant, 7 kg	660*	20†	0.76	0.38	0.54	2.55	1.02	0.51	1.01	0.52	0.97	0.18
Infant, 10 kg	1100*	35†	1.26	0.63	0.90	4.25	1.70	0.85	1.7	0.87	1.61	0.30

* *Calorie Requirements*, FAO, 1950.

† *Recommended Dietary Allowances*, N.R.C. U.S.A., 1948.

Amino Acid Requirements: Albanese, A. A., *Protein and Amino Acid Requirements of Mammals*, 1950.

TABLE III

Comparison of 100 gm of Whole Wheat Mixed with (a) 35 gm Skim Milk, (b) 50 gm Pulses, or (c) 15 gm Fish Meal, with the Calorie, Protein, Amino Acid Requirements of 6-kg Infant

	Calo-ries	Pro-tein	Argi-nine	Histi-dine	Isoleu-cine	Leu-cine	Ly-sine	Methionine	Phenyl-alanine	Threo-nine	Valine	Trypto-phan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Requirements 6-kg infant	660	20	0.76	0.38	0.54	2.55	1.02	0.51	1.01	0.52	0.97	0.18
100 gm whole wheat, soft	333	10.5	0.48	0.24	0.45	0.79	0.30	0.28	0.57	0.37	0.48	0.14
100 gm whole wheat, plus 35 gm dry skim milk	459	23.1	1.00	0.56	1.37	2.15	1.37	0.67	1.25	0.95	1.34	0.49
100 gm whole wheat, plus 50 gm pulses	505	21.6	1.26	0.48	1.06	1.57	1.02	0.39–0.61	1.13	0.80	1.09	0.23
100 gm whole wheat, plus 15 gm fish meal	388	21.5	1.39	0.53	1.11	1.81	1.37	0.57	1.06	0.94	1.20	0.23

TABLE IV

Comparison of 200 gm of Whole Wheat Mixed with (a) 35 gm Skim Milk, (b) 50 gm Pulses, or (c) 15 gm Fish Meal, with the Calorie, Protein, Amino Acid Requirements of 10-kg Infant

	Calo-ries	Pro-tein	Argi-nine	Histi-dine	Isoleu-cine	Leu-cine	Ly-sine	Methionine	Phenyl-alanine	Threo-nine	Valine	Trypto-phan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Requirements 10-kg infant	1100	35	1.26	0.63	0.90	4.25	1.70	0.85	1.7	0.87	1.61	0.30
200 gm whole wheat	666	21	0.96	0.48	0.90	1.58	0.60	0.56	1.14	0.74	0.96	0.28
200 gm whole wheat, plus 35 gm dry skim milk	792	33.6	1.48	0.80	1.82	2.94	1.67	0.95	1.82	1.32	1.82	0.46
200 gm whole wheat, plus 50 gm pulses	838	32.1	1.74	0.72	1.51	2.36	1.32	0.67–0.93	1.70	1.17	1.57	0.42
200 gm whole wheat, plus 15 gm fish meal	721	32	1.87	0.77	1.56	2.60	1.67	0.85	1.63	1.31	1.68	0.37

maize (Table VI). We have also made some calculations in the event that more pulses, milk, or fish flour would be used (on a comparable protein basis) in combination with cereals (Table VII).

From Table I, it can be seen that relatively small quantities of dry skim milk, pulses, or fish meal (on a comparable protein basis) make large contributions to the provision of essential amino acids, and this holds especially for isoleucine, leucine, lysine, methionine (in milk only), and to a lesser degree, phenylalanine and most of the others; these amounts supplement wheat flour protein very well.

From Table II, it will be seen that the infants have high requirements especially for leucine, lysine, phenylalanine and tryptophan.

If we compare, in Table III, the essential

TABLE V

Comparison of 200 gm of Rice Mixed with (a) 35 gm Skim Milk (b) 50 gm Pulses, or (c) 15 gm Fish Meal, with the Calorie, Protein and Amino Acid Requirement of a 10-kg Infant (About 1 year Old)

	Calories	Protein	Arginine	Histidine	Isoleucine	Leucine	Lysine	Methionine	Phenylalanine	Threonine	Valine	Tryptophan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Requirements 10-kg infant	1100	35	1.26	0.63	0.90	4.25	1.70	0.85	1.7	0.87	1.61	0.30
200 gm white rice	720	13.4	1.01	0.24	0.73	1.15	0.45	(0.42)	0.70	0.53	0.87	0.18
200 gm white rice, plus 35 gm dry skim milk	846	26	1.53	0.56	1.65	2.51	1.52	(0.81)	1.38	1.11	1.73	0.36
200 gm white rice, plus 50 gm pulses	892	24.5	1.79	0.48	1.34	1.93	1.17	(0.53–0.75)	1.26	0.96	1.48	0.27
200 gm white rice, plus 15 gm fish meal	775	24.4	1.92	0.53	1.39	2.17	1.52	(0.71)	1.19	1.10	1.59	0.27

TABLE VI

Comparison of 200 gm of Maize Mixed with (a) 35 gm Skim Milk, (b) 50 gm Pulses, or (c) 15 gm Fish Meal, with the Calorie, Protein, and Amino Acid Requirements of 10-kg Infant

	Calories	Protein	Arginine	Histidine	Isoleucine	Leucine	Lysine	Methionine	Phenylalanine	Threonine	Valine	Tryptophan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Requirements, 10-kg infant	1100	35	1.26	0.63	0.90	4.25	1.70	0.85	1.7	0.87	1.61	0.30
200 gm whole maize	712	19	0.92	0.48	1.22	2.84	0.44	0.58	0.96	0.70	1	0.12
200 gm whole maize, plus 35 gm dry skim milk	838	31.6	1.44	0.80	2.14	4.20	1.51	0.97	1.64	1.28	1.86	0.30
200 gm whole maize, plus 50 gm pulses	884	30.1	1.70	0.72	1.83	3.62	1.16	0.69–0.91	1.52	1.13	1.61	0.21
200 gm whole maize, plus 15 gm fish meal	767	30	1.83	0.77	1.88	3.86	1.51	0.87	1.45	1.27	1.72	0.21

TABLE VII

Comparison of 200 gm of Whole Wheat Mixed with (a) 52 gm Skim Milk, (b) 75 gm Pulses, (c) gm Fish Meal, or (d) 45 gm Skim Milk and 5 gm Fish Meal, with the Calorie, Protein, and Amino Acid Requirements of a 10-kg Infant

	Calories	Protein	Arginine	Histidine	Isoleucine	Leucine	Lysine	Methionine	Phenylalanine	Threonine	Valine	Tryptophan
		gm	gm	gm	gm	gm	gm	gm	gm	gm	gm	gm
Requirements 10-kg infant	1100	35	1.26	0.63	0.90	4.25	1.70	0.85	1.7	0.87	1.61	0.30
200 gm whole wheat	666	21	0.96	0.48	0.90	1.58	0.60	0.56	1.14	0.74	0.96	0.28
200 gm whole wheat, plus 52 gm dry skim milk	853	39.7	1.74	0.96	2.27	3.59	2.19	1.15	2.15	1.60	2.24	0.55
200 gm whole wheat, plus 75 gm pulses	925	37.6	2.12	0.85	1.81	2.74	1.68	0.73–1.06	1.97	1.39	1.87	0.41
200 gm whole wheat, plus 22 gm fish meal	746	37.5	2.30	0.91	1.87	3.08	2.17	0.99	1.87	1.58	2.02	0.41
200 gm whole wheat, plus 45 gm skim milk and 5 gm fish meal	846	41	1.93	0.99	2.31	3.67	2.34	1.17	2.17	1.68	2.31	0.55

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amino acid requirements of the 6-kg infant with the amounts supplied by 100 gm whole wheat flour with one of the additions (of 35 gm dry skim milk, 50 gm pulses, or 15 gm fish meal, without which all essential amino acid supplies would fall short), we see that only the leucine supply falls short for pulses and fish meal. It should be taken into account that in this table the protein needs are covered, but not the needs in calories.

If we now turn to Table IV, and compare with the requirements of a 10-kg infant, we see that with 200 gm whole wheat flour and the same additions as before, the picture is much the same; again, the leucine requirements are not covered, not even by dry skim milk. The protein supply of the three combinations meets the requirements, but the calories do not. More wheat flour or more of one of the three additions is therefore needed.

If one substitutes 200 gm of whole wheat by the same amount of white rice (Table V), pulses and fish flour also are deficient in a number of other amino acids, whereas dry skim milk is deficient only in phenylalanine. Not only are calorie requirements not met, but neither are those for protein. Therefore, such a "white rice diet" should be supplemented with much more of the protein foods under consideration.

If one substitutes 200 gm of whole wheat flour by whole maize (Table VI), only pulses fall short, and then only in lysine.

We realize the very relative value of these calculations, but (quite apart from the "leucine" puzzle) they substantiate to a high degree the supplementary value of the protein of milk, pulses, and fish flour to cereal products.

Summary

The problem of protein malnutrition in many underdeveloped countries calls for the development of appropriate and economical protein-rich foods, particularly in the diet of infants who do not receive adequate amounts of milk. FAO is currently engaged in the development and testing of protein foods designed to meet specific regional needs, and this report on their progress includes data on soy, peanut, pulse-and-milk, and fish products. An analysis of the amino acid content of these foods is compared to the requirements of the infant, to indicate what needs can be met by these products and how they may be completed by complementary foods.

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Editorial

Niacin-Tryptophan Relationships in the Development of Pellagra

Although it is now generally recognized that tryptophan can cure pellagra—and it is interesting to recall that Goldberger and Tanner produced such a cure in 1921[1]—the quantitative relationship of tryptophan and niacin to this end have not been known. Why should Goldberger's[2,3] and Goldsmith's[4] maize diets have produced pellagra and why did the wheat diets of Goldsmith and of the Elgin studies[5] result in no symptoms of pellagra? And why, again, should there be no significant incidence of pellagra in rural Central America,[6] an area where corn with 10 per cent moisture is consumed in amounts as high as 500 gm per day?

Recent studies at Elgin State Hospital on the relative effects of deficiencies of niacin and tryptophan have produced some interesting results which may lead to the better understanding of the so-called pellagragenic properties of corn. Although pellagra was not produced and no appreciable amounts of corn were used in this Elgin project, the data obtained, when considered together with those reported by others, make possible some valuable interpretations.

Three different groups received the same basal diet for almost two years; one group without supplement, one supplemented with 10 mg niacin, and another group with 100 mg tryptophan. By comparing urinary excretions of N^1-methylnicotinamide with the intake of niacin precursors it was possible to make estimates of the relative efficiency with which niacin and tryptophan produced N^1-methylnicotinamide. A ratio of approximately 1:60 was obtained in comparing data from the three experimental groups. This was confirmed when 10 gm of a commercial lactalbumin, providing 200 mg of tryptophan, was given to some subjects from each group.

It is apparent to any investigator that it is not reasonable to assume an inflexible relationship between tryptophan and niacin consumption which could be maintained through all genetic and dietary variations; but it is not unreasonable to make an approximation such as has been suggested in order to facilitate calculations of niacin equivalents. Whether or not the ratio should remain at 1 to 60 will, as with other nutritional standards, need additional evaluation. The data about to be published supporting this ratio are not statistically incontrovertible, as only 30 subjects were involved, but the arithmetical averages obtained do provide a point of reference sufficient for present use. Some support for choosing 60 as the weight in mg of tryptophan equivalent to 1 mg of niacin in human diets can be obtained from the work of Krehl, Sarma, Tepley, and Elvehjem,[7] who showed that in rats 1 mg of niacin in 100 gm of diet could be replaced by 50 mg of tryptophan.

The basal diet in the Elgin study provided 5.8 mg of niacin and 265 mg of tryptophan (considerably less than the estimate of 6.7 mg of niacin and 300 mg of tryptophan in the Goldberger diet). However, the Elgin diet provided only 2300 calories, whereas Goldberger's subjects needed about 3000 calories to replace their energy expenditures. If 60 mg of tryptophan are given a niacin equivalence of one and a calculation is made for the equivalents per 1000 calories, one obtains figures of

4.43 for the Elgin diet and 3.90 for the Goldberger diet. Similar calculations for Goldsmith's "corn" diet (which provided 4.7 mg niacin, 190 mg tryptophan, and approximately 2000 calories), and for Goldsmith's "wheat" diet (which provided 5.7 mg niacin, 230 mg tryptophan, and approximately 2000 calories), give figures of 3.93 and 4.77 niacin equivalents, per 1000 calories, respectively. From this one may summarize that pellagra developed at niacin equivalents of 3.9 but was not apparent at 4.7.

The same calculation cannot be made for the high corn diet used in Central America because of lack of specific information about caloric consumption. Aguirre, Bressani, and Scrimshaw[6] have indicated that the average corn consumption by the Guatemalan Indian is on the order of 500 gm per day. Taking into consideration all corn varieties that they analyzed, this amount would provide an estimated average of 8.8 mg of niacin and 227 mg of tryptophan from corn alone, amounts unlikely to be pellagragenic even on a diet of 2500 calories. This leads to the obvious conclusion that if corn is a sufficiently large proportion of a diet, pellagra will not develop! One should, however, be careful to point out that though corn in sufficient proportions may prevent pellagra, it is not adequate in amino acid composition to preclude other nutritional disorders.

If our suggestions regarding "niacin equivalents" should be valid, then the replacement of about half the corn in the Central American diet with sweet potatoes, corn syrup, corn starch, or other carbohydrate foods, low in protein, should markedly increase the incidence of pellagra in that part of the world. Conversely, if about half the protein foods in a marginal North American diet with little animal protein is provided by corn, then this diet would be pellagragenic if fed for four months or longer.

As very large percentages of corn in diets are less pellagragenic than diets with half as much corn, there seems to be little justification for the practical consideration of a "toxic factor" in corn. This elimination of the "toxic factor" does not exonerate corn as the culprit in human pellagra, because, without corn, it is difficult to conceive of a practical diet that has sufficient calories and protein for minimal maintenance and has a niacin equivalence of less than 5.0. The alcoholic who develops pellagra ingests many calories and takes in little protein of any kind.

The implication that more corn (and less carbohydrate) will prevent pellagra should provide a basis for some interesting investigations.

At this point it may be pertinent to note that cow's milk is low in niacin,[8] 1.21 mg per 1000 calories, but high in tryptophan,[9] 673 mg per 1000 calories, and that human milk in comparison has 2.46 mg of niacin and 443 mg of tryptophan per 1000 calories, respectively.

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Sir Edward Mellanby (1885–1955)

The death of Sir Edward Mellanby—a corresponding editor of this JOURNAL—removes an historical figure from the field of nutritional research in Britain. He was born a north-country Englishman. An athlete in his youth, he gave up sport on entering Cambridge University and published his first paper (on creatine) while still a medical student. With the support of Gowland Hopkins he began to study rickets and in 1918 succeeded in producing it experimentally in puppies. He was inclined at first to attribute it to lack of the fat-soluble vitamin (A) described as a growth factor five years previously by McCollum and Davies. But once experimental rickets had been produced, the distinction between vitamin A and vitamin D quickly followed. Mellanby continued to be interested in the reason why cereals (and especially oatmeal) encourage the production of rickets. The culmination of his research on this subject was his identification in 1937 of phytic acid as the substance in cereals that interferes with the absorption of calcium from the gut. This opened the way to the modern study of vitamin antagonists. He made important experiments on the effect of vitamin A deficiency on the growth of the skeleton, and elucidated the mechanism whereby the nerve roots of the spinal cord may be damaged by irregular development of the bones. Then, in 1947, he announced the surprising discovery that fits in dogs are caused by a toxic substance produced in the agene process of bread-making; this opened up in Britain the whole important subject of potentially poisonous substances that may find their way into food.

In 1933 Mellanby became Secretary of the (British) Medical Research Council. For any lesser man this would have spelled the end of research and the beginning of a busy life of full-time administration. Yet Mellanby continued his own research throughout the whole time of his tenure of this arduous office. At weekends he would leave the M.R.C. offices in London and travel to the quiet seclusion of his own laboratory in Sheffield. The M.R.C. did not suffer. Mellanby's belief was that in so far as research can be organized at all, it is best that it should be organized by someone actively engaged in it. Under his guidance the M.R.C. was nourished through its period of adolescence into the adult giant that it is today. The increasing interest of the Welfare State in medical research made the growth of this organization inevitable, but the particular way that it has grown is in no small part due to Mellanby. One unique feature, which may well be envied in the United States, is that although the Council administers public funds, it is not directly answerable to the politicians in the House of Commons in its use of them.

In the 1930's Mellanby was also active in international work on nutrition. As chairman of the Technical Commission on Nutrition of the League of Nations, he did much to promote the international standardization of vitamins and the publication (in 1936) of the first agreed standards for dietary requirements.

The outbreak of the Second World War brought a huge load of new responsibilities. Mellanby stayed at his desk in bomb-damaged Westminster, accessible to everyone concerned with the special medical problems of war. At such interviews his manner was blunt and sometimes impatient; yet behind it there was always a background of kindly humor. A few short, shy, sensible words sent the visitor away encouraged. The achievements of the M.R.C. during the war have since been fully reported; they include the scientific control of feeding a country during a time of threatened siege. Through the Scientific Food Policy Committee of the War Cabinet Mellanby exerted a strong influence on the introduction of such measures as the fortification of margarine with vitamins A and D and the addition of calcium to the wartime loaf of bread. He was also chairman of the Food Rationing (Special Diets) Advisory Committee which, throughout the period of rationing, ensured the cooperation of the medical profession by granting special rations to patients under treatment. It was fortunate indeed that the Secretary of

the M.R.C. at this time had a lively personal interest in nutrition.

The War left Mellanby a tired man. It was therefore a happy idea on the part of Vanderbilt University to invite him to Nashville as a visiting lecturer. This visit he hugely enjoyed. He returned to Britain relaxed and benevolent, with all his war-time troubles shed. As he himself said to the present writer: "They taught me how to laugh again."

With his retirement from the M.R.C. in 1949, he devoted his time to his old love, research. At the M.R.C. Nutrition Laboratory, Mill Hill, which he himself had done so much to create, he died suddenly on Sunday, January 30, having been engaged in an experiment an hour before.

He is survived by his wife, Lady May Mellanby, who herself has made important contributions to the study of nutrition, notably in connection with dental health.

—A. P. MEIKLEJOHN, M.D.
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Scotland

Letter to the Editor

IN REPLY TO COMMENTS IN *Nutrition Reviews*

Dear Sir:

A recent report from this laboratory (J. CLIN. NUTRITION 1: 224, 1953) was the subject of comment[1] which, it seems to us, may lead to misunderstanding unless the points raised are specifically answered.

The writers of the review[1] infer that adequate nutrition in terms of good muscle mass, nitrogen equilibrium, or weight equilibrium, is impossible on diets containing only protein and fat. In Figure 1 is shown a long-term balance study in an elderly male who was maintained for more than six months on a formula diet in which the caloric sources were entirely protein and fat. Without any hormonal therapy, nitrogen and weight equilibrium were achieved, followed by weight gain and positive nitrogen balance during the administration of anabolic steroid hormones. These and other similar data are included in papers dealing with the evaluation of specific anabolic steroids and with pituitary growth hormone.[2,3]

Regarding the statement in the review: "The palatability and the practicability of a high fat-high protein diet has been repeatedly examined with human subjects, and in each instance found unsatisfactory"—there is no question that a diet containing only protein and fat would have little to recommend it, from the standpoint of palatability. Fortunately, the presence of amounts of carbohydrate sufficient to provide for palatability are still thoroughly compatible with major falls in serum cholesterol when suitable mixed diets are used. By way of illustration of this statement, in Figure 2 is shown the change in serum cholesterol and phospholipids in a severely diabetic patient maintained on a mixed diet containing large amounts of vegetable fat, who over a period of about one month had a decrease in serum cholesterol levels of approximately 400 mg per 100 ml.

It has been said that physical intolerance, with ketosis, rather than anorexia, prevents the success of this diet. In Figure 3 is shown a study designed specifically to bring out the "antiketotic effect of protein" under quantitatively controlled conditions on the metabolic ward. From this it is apparent, as one would expect in view of the relatively small amount of carbohydrate necessary to "turn the metabolic wheel," and the amount of carbohydrate which can be derived from protein, that protein would be a perfectly satisfactory substitute for carbohydrate in an antiketotic sense, so long as one has a proper balance of protein and fat.

Also not mentioned in the review was the fact that Ahrens *et al.* at the Rockefeller Institute have fully confirmed our observations regarding the profound decrease in serum cholesterol and phospholipids in patients maintained on high intake of vegetable fat.[4,5]

More recently further confirmation has come from Beveridge *et al.*[6] Whether the decrease in serum cholesterol, which one can obtain predictably with a high vegetable fat, nutritionally adequate diet, is good, bad, or indifferent for people with vascular disease, only a great amount of time and work will determine. We have been at some pains to point this out.

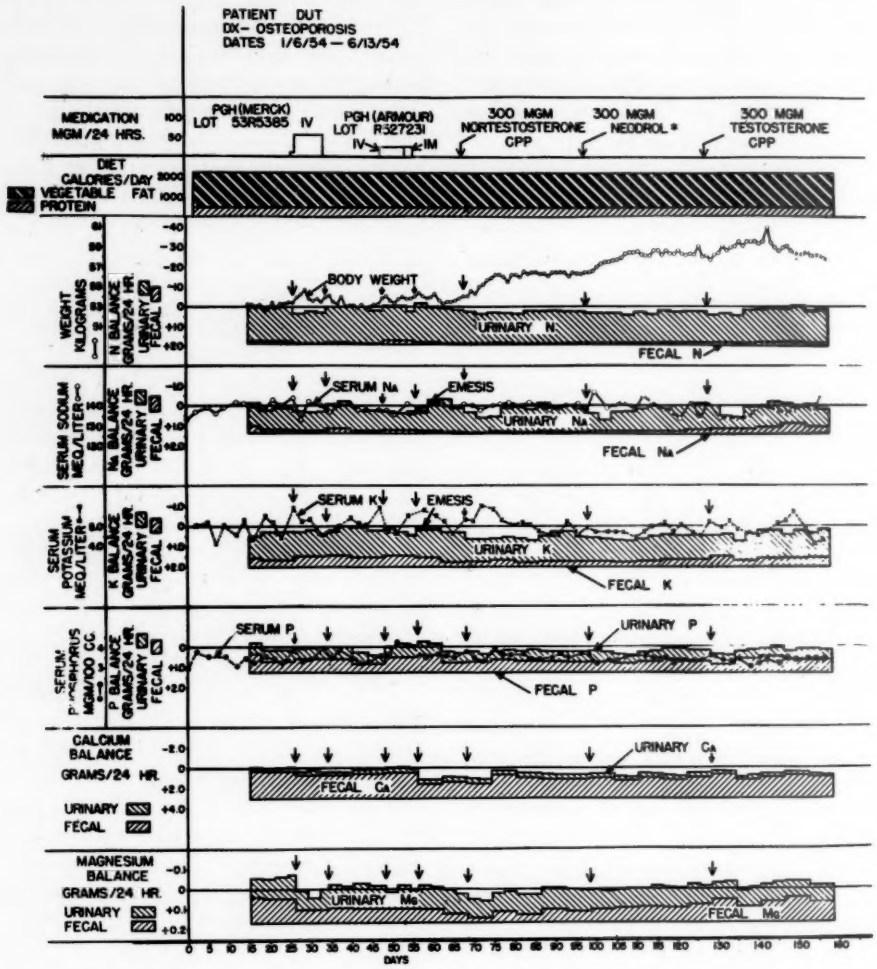

Fig. 1. Balance studies using formula diets containing only protein and fat (supplemented with essential vitamins and minerals).

As to the comments in the review regarding Tween-80, cerebrosides, etc., it is obvious that the mixed diets, which will produce as great a fall in cholesterol as the formula diets, contain no added emulsifying agents of any sort. Further, in Figure 4 is a study in which precisely the same emulsifier was added to formulae containing identical amounts of protein, fat, and carbohydrate, the fat at different periods being of animal and vegetable origin, respectively. The differential effects produced by the two sources of fats, in regard to serum cholesterol, require no comment.

The method used for determination of plasma cholesterol is that of Michaels.[7] In

Figure 5 are shown random plasma determinations compared with "classical" Schönheimer-Sperry determinations on the same plasmas. Except for the final colorimetry, the methods

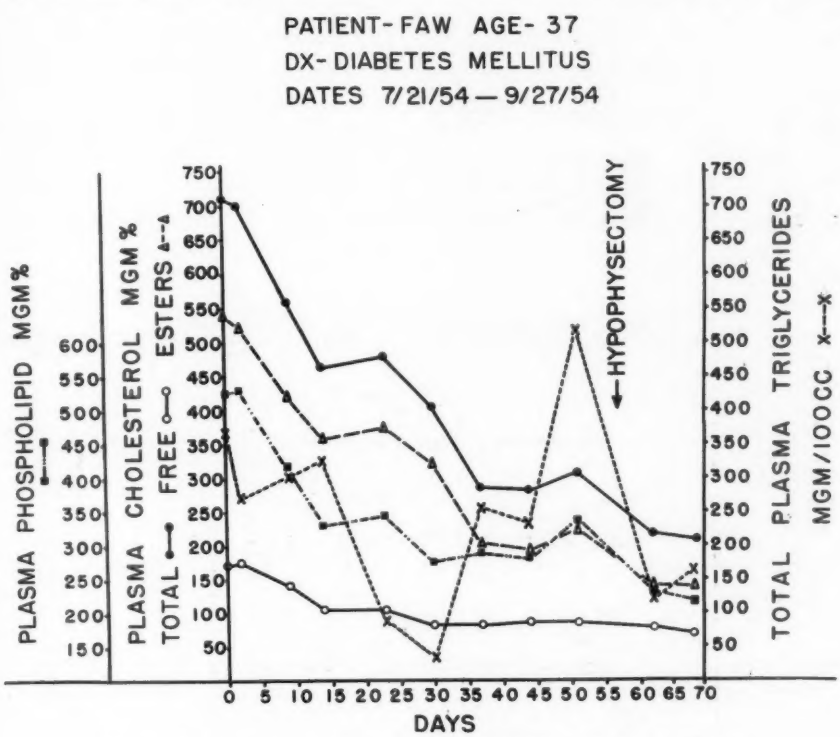

Fig. 2. Fall in serum lipids on non-formula, high vegetable lipid diet.

are essentially identical. The Michaels procedure in this regard appears to have certain advantages.

We wish to summarize our present views again.

1. Formula and mixed diets containing large amounts of vegetable fat consistently and predictably produce a profound fall in serum cholesterol and phospholipids, as compared to the levels obtained with diets containing equal amounts of fat of animal origin.

2. We are still unable to explain the mechanism of this differential effect. It is probable that the lack of cholesterol in vegetable fats is in a measure responsible. Some of the data, however, suggest the possibility that vegetable fats contain some substance(s) which have some specific effect upon cholesterol metabolism. It is entirely possible that both factors may play a part.

3. We, in common with everyone else, are still unable to say with any certainty that a low blood cholesterol is good, bad, or indifferent insofar as the production or progression of vascular disease in any given individual is concerned. Until we know more, however, it seems reasonable to us to accept the concept that a low or normal level is preferable to a high level.

4. On the basis of a rather vast number of observations, we can state without any hesitation that excellent nutrition can be maintained on formula diets containing only fat and protein (reinforced obviously with other essential nutrients, but free of carbohydrate), and with mixed diets which are high in fat and protein, and low in carbohydrate. We have yet to find a diet which can be considered in any sense of the word palatable which does not contain a reasonable amount

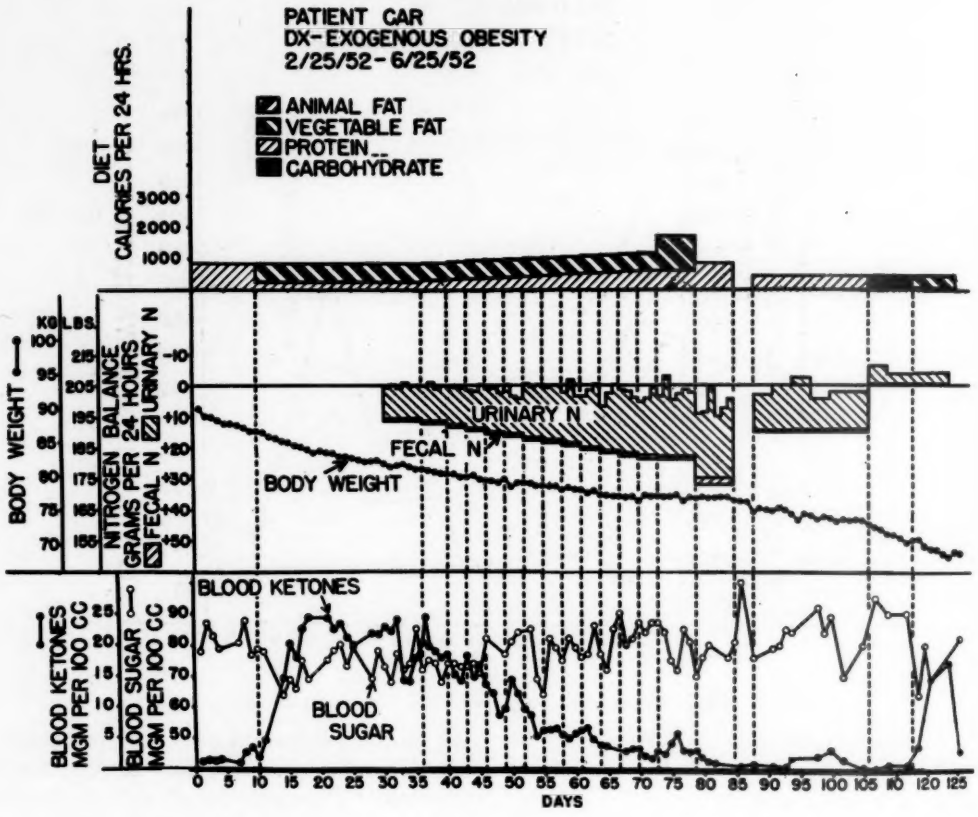

Fig. 3. Quantitative aspects of the antiketotic effects of protein. It appears in this patient (whose estimated daily caloric requirement was 1700 calories) that the amount of catabolized protein necessary to maintain a blood ketone level below 5 mg per 100 ml was of the magnitude of 125 g per day. This was so, essentially, regardless of the level of fat intake. However, when only protein was fed, less than 100 g of *catabolized* protein maintained comparable blood ketone levels.

This latter observation may indicate: (1) Greater efficiency of metabolism of endogenous as compared to dietary fat and/or, (2) Decreased total metabolism during the period of low calorie intake (days 87–106) with consequent decrease in the amount of fat catabolized; and, therefore, a decrease in the amount of non-fat calories necessary to "turn the metabolic wheel."

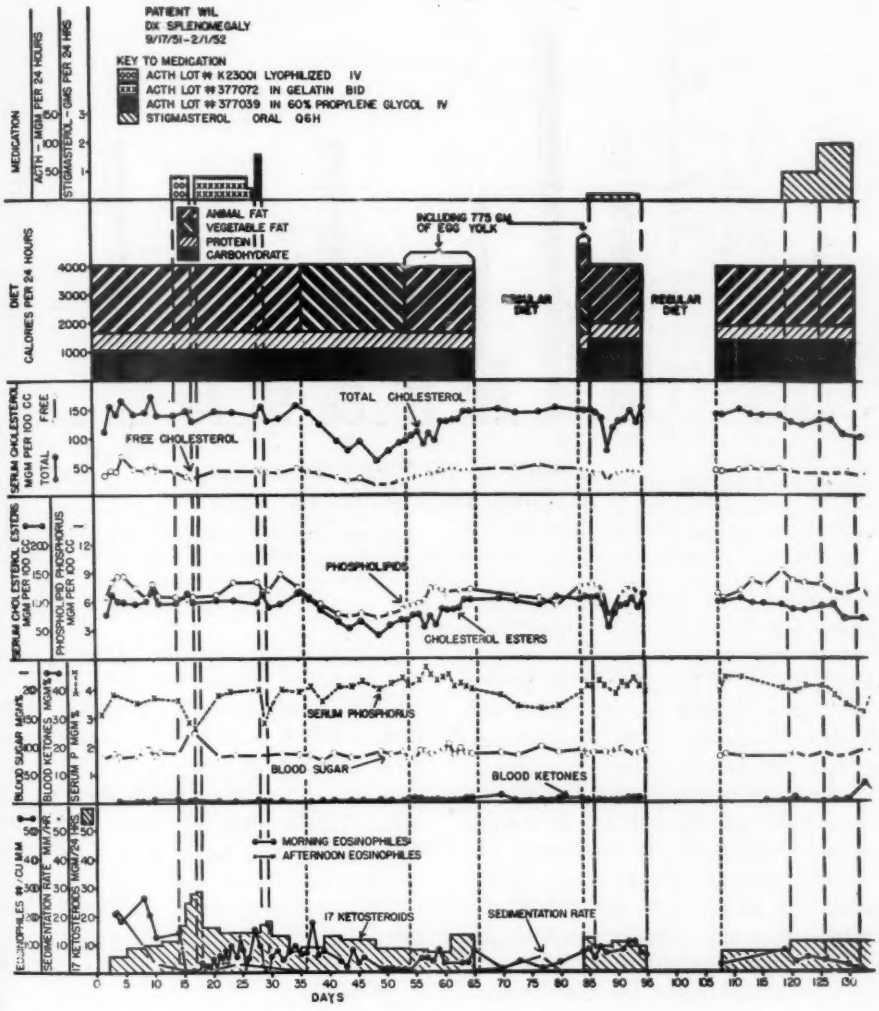

Fig. 4. Comparative effects of calorically equal amounts of animal and vegetable fat. The emulsifying agents were identical in each instance.

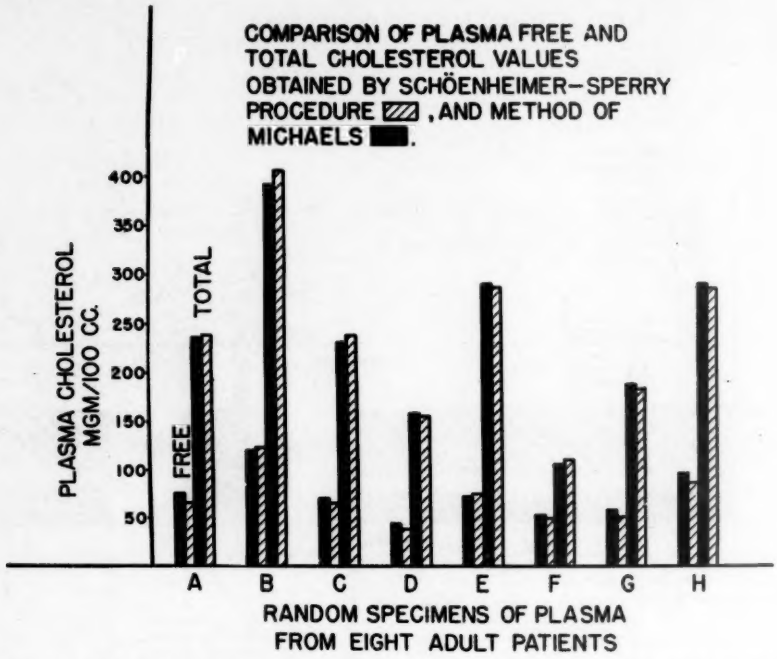

Fig. 5. Comparative free and total plasma cholesterol values, as determined by the Schönheimer-Sperry, and Michaels methods.

of carbohydrate. We do not expect to find such a diet, nor do we see any major reason to search for one.

5. Depending upon the amount of protein in the diet, patients may be maintained with little or no hyperketonemia on formulae containing only fat and protein as sources of calories. In other words, protein in sufficient amount is quite as efficient an antiketotic agent as is carbohydrate. In this connection, it may be well to point out that levels of blood ketones as high as 20 to 25 mg/100 ml are apparently compatible with excellent health. In the mixed high vegetable lipid diets used clinically in this institution, the blood ketone levels rarely exceed two mg/100 ml.

—Laurance W. Kinsell, M.D., Director
—George D. Michaels, PH.D., Senior Research Biochemist
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Addendum

A recent report by Best, Duncan, Wathen, VanLoon, and Shipley,[8] as well as other previous reports, indicates that β-sitosterol will produce a fall in serum cholesterol, presumably by its inhibiting effect upon cholesterol absorption or re-absorption from the intestinal tract. In our hands, sitosterol as well as some other derivatives of vegetable fat have on occasion produced such an effect. Such changes, however, have not been consistent, and have never been of the magnitude noted during the administration of large amounts of vegetable fat.

Until recently, all of the vegetable fats which we have used have been high iodine number fats, e.g. soy, corn, and peanut oil. To determine whether the unsaturated fatty acid content of vegetable fat might have any bearing upon the lowering of plasma cholesterol and phospholipids, a comparative evaluation of vegetable fats of high, medium, and low iodine numbers has been carried out. As

shown in Figure 6, the effect upon the level of serum cholesterol and phospholipids appears to be related directly to the unsaturated fatty acid content of the fat. Studies to determine the mechanism of this effect are now being undertaken.

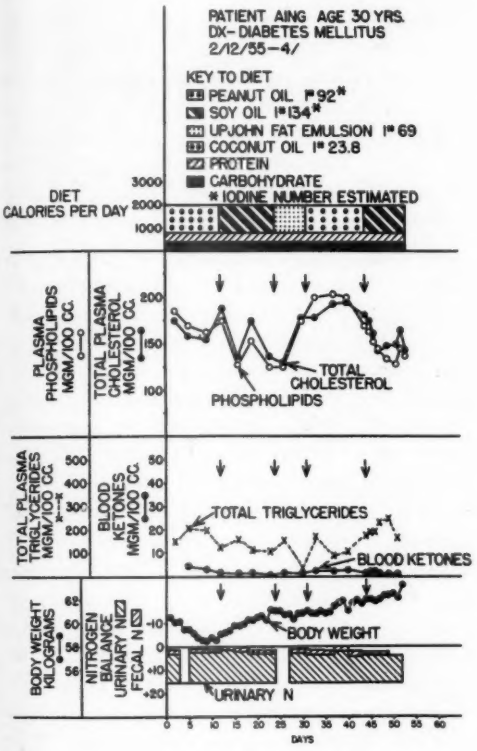

Fig. 6. Comparative effects of different vegetable fats upon the plasma cholesterol and phospholipids. From this study, it appears that the ability of vegetable fat to lower plasma cholesterol is associated with its unsaturated fatty acid content.

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Dietotherapy

NUTRITION OF CHILDREN DURING THEIR SCHOOL YEARS

By Anna de Planter Bowes, M.A.*

On January 19, 1955, the Census Bureau released the following statement: *Our children set mark: 36 million go to school.* This figure is the estimate of enrollments in schools and colleges in October 1954. A breakdown of this enrollment was stated as follows:

in kindergartens	1,500,000
in elementary schools	24,400,000
in high schools	7,700,000
in colleges	2,400,000

These 36 million individuals constitute the most vital segment of the nation for nutrition education.

From the time a child enters the kindergarten until he leaves school, his nutrition and his health are a concern of many people and agencies. In addition to the parents and the family physician and dentist as early guardians of the child's health, a team of workers is available to safeguard and promote good nutrition.

The classroom teacher has the greatest opportunity to make good food and health habits *vital* in the thinking and practices of children. Her day-to-day influence is greatest among the younger children in kindergarten and the lower elementary grades. In the upper grades, the school nurse, dental hygienist, physician, dentist, psychologist, nutritionist, home economics teacher, the lunch room manager, science and health teachers, and the coach of athletic teams each and collectively have their varying spheres and degrees of influence among the older pupils.

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Obviously, best results are obtained when each of the many participants has correct and up-to-date information on this dynamic subject of nutrition. This is a responsibility of the teacher and other professional training institutions at the undergraduate and graduate levels. Refresher courses and summer workshops are a helpful bridge to current facts and procedures for older teachers. Also, it is important that the school and community work together in developing programs based on nutrition in its broader sense. This recognizes the interrelation of physical, emotional, and social development. It also recognizes Graham Lusk's (1917) definition of nutrition as "the sum of the processes concerned in the growth, maintenance, and repair of the living body as a whole or of its constituent parts." While food is an exceedingly important part of nutrition, many other factors influence growth, such as emotions, sleep and rest, exercise, fresh air, and sunshine.

Dietary Essentials During Growth

National and international groups have formulated numerous dietary standards for individuals of different ages and for population groups. Since 1940 the Food and Nutrition Board of the National Research Council has accepted the responsibility for developing a dietary standard for the United States. Maintenance of *good nutrition* rather than the minimal needs of any age group is the basic philosophy and objective of the recommendations made. The last revision of the Board, comprised of approximately 50 of the country's leading scientists and nutrition research workers, was published in 1953. The recom-

mendations for children from kindergarten age through the early college years are outlined in Tables I and II.

TABLE I

Recommended Daily Dietary Allowances

Ages	Calories	Protein	Calcium	Iron
		gm	*gm*	*mg*
Children				
4–6 years	1600	50	1.0	8
7–9 years	2000	60	1.0	10
Boys				
10–12 years	2500	70	1.2	12
13–15 years	3200	85	1.4	15
16–20 years	3800	100	1.4	15
Girls				
10–12 years	2300	70	1.2	12
13–15 years	2500	80	1.3	15
16–20 years	2400	75	1.3	15

TABLE II

Recommended Daily Dietary Allowances

Ages	Vitamin A	Thiamine	Riboflavin	Niacin	Ascorbic acid	Vitamin D
	IU	*mg*	*mg*	*mg*	*mg*	*IU*
Children						
4–6 years	2500	0.8	1.2	8	50	400
7–9 years	3500	1.0	1.5	10	60	400
Boys						
10–12 years	4500	1.3	1.8	13	75	400
13–15 years	5000	1.6	2.1	16	90	400
16–20 years	5000	1.9	2.5	19	100	400
Girls						
10–12 years	4500	1.2	1.8	12	75	400
13–15 years	5000	1.3	2.0	13	80	400
16–20 years	5000	1.2	1.9	12	80	400

Calories

The calories listed for the various ages are a *first* need for meeting the high energy and growth requirements of active children and youth. In earlier tables, no distinction was made between the sexes until 13 years of age. However, in the United States, there seems to be a greater energy requirement for boys than for girls of the 10- to 12-year age group. Boys engage in more strenuous games and they also expend more energy than girls of the same age and body build in the same activities.

Adequate caloric allowances for adolescents are not easily decided. Rate of growth, final body size, as well as activity, are important considerations for individuals. Selections of foods which provide body-building nutrients as well as calories are top priorities to prevent or correct the undernutrition and overnutrition prevalent during these years. Much educational effort is justly being directed against snack or mealtime foods which provide only "empty calories."

Protein

After 10 years of age, protein needs are higher than those of normal adult men and women. This fact is often not well understood by parents, teachers, lunchroom managers, and youth. Careful meal planning at home and at school is necessary to secure a regular, *daily* adequate intake of protein. At least half of the dietary protein should come from animal sources. Adequate protein at *each meal* gives satiety values that are exceedingly important. The feeling of being "well fed" can be a large determining factor in a child's craving for sweets—so often a source of empty calories—and also a potential or actual contributor to dental caries.

Calcium

Only one change was made in the calcium figures in the revised Dietary Allowances. Because of ability to use increased calcium in late adolescence, demonstrated by girls as well as boys, the allowance for 16- to 20-year-old girls was increased from 1.0 to 1.3 grams per day. This increase has practical significance for good nutrition and skeletal maturation.

Today's trend is that many more girls are marrying and becoming mothers at earlier ages than formerly. Good nutrition prior to pregnancy is always a health asset to mother and child. It has extra significance when pregnancy is superimposed on a body not yet completely mature.

Iron

Many studies have been done in recent years on the iron needs of children of different ages. The allowances listed in Table I appear to be the best recommendations at this time. Research points up the fact that deficiencies of other nutrients such as protein, calcium, and vitamin C may increase the body's need for iron for normal hemoglobin. Anemia is apparently prevalent among children of all ages. More adequate total food intake appears just as important as adequate iron. This is particularly true during adolescence.

Vitamin A

No changes were made in the revised Dietary Allowances for this vitamin. As the body can store vitamin A, there is much practical value in emphasizing rich food sources all during growth. The role of vitamin A in promoting growth, in tooth enamel formation, and in dark adaptation are significant reasons for checking its adequacy during school years.

The B Vitamins

Minor changes were made in thiamine, riboflavin, and niacin allowances of children at various ages—consistent with changes in caloric allowances.

Continuing refinement of foods, newer methods of food processing, and high intake of refined sugars endanger the adequacy of the B vitamins in the meals of many children. This is particularly true among overweight individuals whose normal cereal and bread intake has been lowered to reduce calories. Enriched bread and cereals are very important contributors to the B vitamins in children's meals.

Ascorbic Acid

The food of younger children is usually adequate to meet allowances of ascorbic acid. Among older children and adolescents, clinical tests show many deficiencies. Dislike for or inability to buy citrus fruits in adequate amounts are important contributing factors.

Vitamin D

Unless Vitamin D milk or fish liver oil in some form is taken during the fall and winter months in the central and northern parts of the United States, diets will fall far below the recommended 400 IU of vitamin D per day for those from 4 to 20 years of age. The value of fortified milk and use of the fish liver oil should be emphasized by the family physician and dentist as well as by schools.

Table III indicates how well-chosen foods can contribute to these Recommended Allowances. Late adolescence was selected because of its very high food needs. Younger children can use this same or a similar pattern. Smaller servings or amounts of meat and fats will help to bring protein and calories to the recommendations for younger children.

TABLE III

DIETARY ADEQUACY DURING LATE ADOLESCENCE

Some Suggestions for a Day's Food Needs

1 quart whole milk
1 to 2 eggs
5 to 6 ounces meat, poultry, or fish
1 whole orange or ½ grapefruit
1 serving other fruit
2 medium potatoes
2 servings leafy, green or yellow vegetable
1 serving other vegetable
1 serving wholegrain or enriched cereal
6 slices wholegrain or enriched bread
3 to 4 tablespoons butter or margarine for bread and vegetables
1 to 2 tablespoons salad dressing
1 to 2 servings peanut butter or dried peas, beans, or lentils at least 3 or 4 times a week
1 serving milk or fruit dessert
1 serving cake or cookies
1 to 2 tablespoons sugar, molasses, honey for cereal or fruit

Calculated values of foods listed: Calories, 3800; protein, 100–110 gm; fat, 160–180 gm; carbohydrate, 400–450 gm; calcium, 1.8 gm; iron, 18 mg; vitamin A, 19,600 IU; thiamine, 2.1 mg; riboflavin, 3.1 mg; niacin, 20 mg; ascorbic acid, 149 mg; vitamin D, 51 IU.

A comparison of these values with the Recommended Allowances for a boy 16 to 20

years shows excellent coverage of all essentials except vitamin D. The regular use of vitamin D milk is one of the easiest ways to raise this vitamin during the winter months when sunshine is very limited. The daily use of a fish liver oil capsule is another recommendation of many physicians during winter months in the central and northern states for vitamin D adequacy.

MEALS FOR ONE DAY FROM SUGGESTED FOODS

Breakfast

1 whole orange
1 serving oatmeal—sugar
1 egg
1 to 2 slices bread or toast with butter or margarine
8 to 12 ounces milk to drink and with cereal

Lunch or Supper

1 serving split pea soup
1 ham and lettuce sandwich
1 piece iced cake
8 ounces milk

Dinner

1 large serving beef with gravy
2 potatoes
1 serving carrots
1 serving snap beans
Lettuce salad with Russian dressing
1 to 2 slices bread with butter or margarine
6 to 8 ounces milk
1 serving caramel cornstarch pudding

Additional Food at Meals or Between Meals

Peanut butter sandwich
Apple
6 to 10 ounces milk

Dietary and Nutritional Status Studies

During the past two decades many data have been assembled on food habits of school children of different age periods and their nutritional status. Through medical examinations, dietary surveys, and detailed clinical studies at research centers, facts are available from practically every state in the nation. Physicians, dentists, and research workers report a high percentage of unfavorable physical conditions closely related to dietary inadequacy. Those most frequently noted are extensive dental caries, poor skeletal development, underweight, overweight, anemia, constipation, and various skin, eye, and tongue conditions associated with vitamin deficiencies. Facts are similar in urban, small town, and rural areas.

The economic level of the family or area was found to be an important factor in the *number* and *degree* of nutrition defects and the rate of their correction. In general—the higher the economic status, the better the medical and dental care, the nutritional status, and the quality of the diets. However, 58 per cent of the children in the highest economic level had diets that needed improvement.

With respect to *food intake*, surveys showed that only 35 per cent of children had good diets when economic levels were not considered. Availability of food did not guarantee a good diet. On the whole, boys ate better than girls. They drank more milk and ate more eggs. Girls ate more green and yellow vegetables. Boys and girls ate about the same amount of meat, potatoes, breads and cereals, butter and margarine.

Analyses of research reports on the basis of deficiencies indicate these facts:

1. Nutritional status and dietary adequacy is, in general, at higher levels for children 4 to 6 years than for children 7 to 12 years. The 13 to 15 age level showed the greatest deviations from good nutritional status and dietary adequacy.

2. Vitamin D was the single most deficient essential nutrient from age 4 to 20 years.

3. The highest deficiencies of other essentials were in *calories* and *thiamine* for both boys and girls at the teen-age level.

4. Teen-age girls were also lower in *iron* and *calcium* than children of either sex at other age periods.

5. About half the children at all age levels were deficient in *ascorbic acid*.

6. Protein was adequate in 83 per cent of children in the younger age group, 67 per cent of the 7 to 9 year old children, 73 per cent of the 10 to 12 year olds, in 57 per cent of teen-age boys and 47 per cent of teen-age girls.

Summary

Carefully prepared and accepted "yardsticks" are available for evaluating good nu-

tritional status and dietary adequacy of school children. The most recent data on the dietary essentials needed have been presented, as well as some suggestions for meeting recommendations in late adolescence—when needs are highest.

Cumulative data from all areas of the country show that much improvement is desirable in both nutritional status and dietary habits.

A *good breakfast* before going to school is still an important goal for children at all ages. Parents feel this is their greatest single difficulty in helping their children to better nutrition. Physicians, nutritionists, dietitians, and school personnel can do much to motivate children of all ages to appreciate the value of this meal. Better breakfasts would eliminate so many problems now faced by teachers, school nurses, and youth itself.

The rapidly expanding school lunch program provides unlimited possibilities for improved nutrition and for better food habits and attitudes on the part of all school children. The many values of a well-operated school lunch program deserve the best support the school and community can provide. A satisfying lunch is an excellent aid to reducing the amount and kind of snack foods children eat when their previous meal is inadequate. Too often, the snacks selected are foods high in carbohydrate and sources principally of "empty calories."

Family and school physicians are highly valued members of the team working for better nutrition. Their emphasis on milk, leafy green and yellow vegetables, on fruits, eggs, and meat, as *necessary* foods for growth, is needed and appreciated by parents and the school faculty.

Motivation to practice good food habits is a continuous educational process all through the years of growth. Here again the team approach can be very helpful. Children, like adults, are not usually motivated by an interest in nutrition as such. They want only the things nutrition can do for them.

The school and community can provide many opportunities to portray *What Nutrition Can Do for You.* Animal nutrition studies, 4-H or FFA projects, school or home gardens, home economics and science class programs all can demonstrate the magic of food in growth and development. Radio and television are powerful media for both education and motivation. Teamwork of all forces in the community needs no finer goal toward which to unite effort than *Better Nutrition for School Children.*

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Nutrition News

☆ News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the JOURNAL.

Optimal Nutrition Conference

A conference on *Optimal Nutrition, Its Analysis and Application* was held on April 8 and 9, 1955, at the George Williams College, Chicago. Titles of sessions included: Basic Science in Optimal Nutrition (Paul R. Cannon, Department of Pathology, University of Chicago, Chairman); Some Clinical Aspects of Optimal Nutrition and Its Relation to Tissue Repair and Rehabilitation (A. K. Peterson, Medical Director, R. R. Donnelley & Sons Company, Chicago, Chairman); and Some Clinical Observations on Optimal Nutrition and Resistance to Toxic Factors (Ben L. Boynton, Rehabilitation Institute of Chicago, Chairman).

Gordon Research Conferences

The 1955 Gordon Research Conferences, to be held this summer in New London, New Hampshire, will include sessions on "Vitamins and Metabolism" and "Food and Nutrition."

The session on "Vitamins and Metabolism" (Paul L. Day, Chairman; Karl Folkers, Vice-Chairman) will be held from August 15 to 19. Among the topics to be considered are:

Nutritional and Metabolic Aspects of Kwashiorkor (Nevin S. Scrimshaw).

Intrinsic Factor and its Relation to Vitamin B_{12} (Robert F. Schilling).

Induced Pantothenic Acid Deficiency in Man (William Bean).

Specific Amino Acid and Vitamin Requirements of Normal and Malignant Cells in Tissue Culture (Harry Eagle).

Review of the Present Knowledge of Functions of Thioctic Acid (George W. Kidder).

The program on "Food and Nutrition" (Anthony A. Albanese, Chairman; Robert A. Harte, Vice-Chairman), scheduled for August 22 to 26, will be divided into sessions dealing with "Amino Acid Needs and Utilization" (James B. Allison, Chairman); "Nutrition and Calorie Limitations" (Henry B. Hass, Chairman); "Parenteral Nutrition" (Harry L. Fevold, Chairman); "Appraisals of the Hazards of Food Additives" (Bernard F. Oser, Chairman); "Food Energy—Yield and Expenditure" (Harry Spector, Chairman); "Fat Utilization" (Daniel Melnick, Chairman); and "New Developments in Dehydrated Foods" (John H. Nair, Chairman). Among the papers presented at these sessions will be:

Hunger and Food (J. R. Brobeck).

Nutritional Balance in Reduction Diets (S. Lepkovsky).

Intravenous Fructose and Invert Sugar Solutions (J. H. Roe).

Intravenous Fat Emulsions (M. I. Grossman).

Postoperative Parenteral Nutritional Needs (C. O. Rice).

Energy Expenditure in Everyday Life (R. Passmore).

In Future Issues:

SYMPOSIUM ON THE ANTIMETABOLITES

SERUM VITAMIN A LEVEL: A CRITIQUE OF METHODS AND SIGNIFICANCE
W. O. Caster and Olaf Mickelsen

REPRODUCTION AND OBESITY
E. M. Widdowson

HUMAN DIETARY DEFICIENCY OF VITAMIN B_{12}
F. Wokes, J. Badenoch, and H. M. Sinclair

Abstracts of Current Literature

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NUTRITION AND THE HEART

The function of the heart is affected both directly and indirectly by changes in the nutritional status of the individual. Nutritional deficiencies alter the metabolic demands of the peripheral tissues, and this affects the cardiac output; at the same time, the contractile force of the myocardium may be altered by a change in the energy-producing mechanisms or in the muscle proteins themselves. The former condition would tend to increase the work of the heart, while the latter will reduce the capacity of the organ to maintain its output. The effect of cardiac decompensation upon the nutritional aspects of human metabolism remains an important topic for investigation.

Urinary Elimination of Total Riboflavin during Cardiac Decompensation. II. Influence of Cocarboxylase on Riboflavinuria in Decompensated Subjects. R. Boldrini and P. Montenero. *Acta vitaminol.* 8: 3, 1954.

The authors had previously demonstrated a marked increase in urinary riboflavin excretion during treatment with digitalis, together with a rise in blood lactic and pyruvic acid levels. Of the alternate explanations considered, the authors preferred the hypothesis that digitalis favored the utilization of phosphorus radicals for the phosphorylation of thiamine. If so, the administration of cocarboxylase (phosphorylated thiamine) to decompensated subjects receiving digitalis should, by providing the organism with the necessary phosphorus radicals for the utilization of thiamine and riboflavin, reduce the excessive loss of riboflavin in the urine.

Six subjects in decompensation receiving a digitalis preparation (0.4 mg of lanatoside C daily) were given a single intravenous injection of diphosphothiamine (100 mg), after which their urinary riboflavin excretion was measured until it had returned to the established basal values. On the day following the injection of cocarboxylase, a sudden fall in urinary riboflavin was observed in all cases. After falling to about 70 per cent of the basal value, it climbed again during the following days to or near the original value.

The data obtained support the hypothesis that the altered riboflavin metabolism in these subjects is the result of interference with the process of phosphorylation. In subjects whose phosphorylation mechanism is defective—either because of a deficiency of phosphorus donors, or because of interference with enzyme systems determining the direction of transphosphorylations—cocarboxylase administration is apparently followed by an elective utilization of riboflavin.—C. J. HOWELL

Beriberi Heart of Alcoholic Origin. L. Langeron. *Presse méd.* 62: 1385, 1954.

A clinical and biologic report is presented of a case of cardiac insufficiency of alcoholic origin, recalling, feature for feature, the cardiac disturbances of beriberi, and which can be termed beriberi heart of alcoholic origin.

The action of vitamin B_1 in particular, administered alone, was spectacular. The peripheral mechanism of this asystolia is discussed. This eventuality is rarely observed in cardiac insufficiency of alcoholic origin, perhaps because the patients are seen too late. —H. GOUNELLE

The influence of such factors as emotions, epinephrine, fluid administration, and other circumstances upon the ventricular repolarization wave has been reported, showing that rapid changes in polarity or amplitude may occur. The ingestion of food is one of the stimuli which may affect the T-wave configuration.

Effect of Eating on Electrocardiograms after Myocardial Infarction. S. M. Levit and B. D. Dinman. *J. A. M. A.* 157: 122, 1955.

Electrocardiograms of 27 patients with acute myocardial infarction were taken before and one-half hour after a hospital meal. A large number of minor and transitory changes were seen in the tracings.

A change in polarity of the T wave (regarded as a major alteration by the authors) was observed in 10 cases. Variations in magnitude, but not polarity, were more frequently observed but would have been of minor significance in interpretation.

The significance of these observations is that unless an electrocardiogram is taken in the fasting state or several hours after eating, erroneous interpretations may be based on T-wave changes in a large number of post-infarction patients.—S. O. Waife

Much speculation centers about the occurrence of hyperglycemia following myocardial infarction or cerebrovascular accidents. In such instances, it is probable that hyperglycemia resulting from such stressful conditions evokes an inadequate insulin response from the pancreatic islets.

The Hyperglycemia of Myocardial Infarction. R. Boulin, P. Uhry, and H. Kaufmann. *Presse méd.* 62: 77, 1954.

The authors measured the blood sugar in five cases of myocardial infarction. The blood sugar may rise transiently to as much as 2.50 g. Even when it remains subnormal, there is a transitory disturbance of glucose regulation.

These disturbances must not lead one to conclude that diabetes is present; they seem to be linked to a chain of phenomena in which there occur, in succession, neurovegetative excitation with discharge of epinephrine, then release of ACTH, and then discharge of glucocorticoids. It is possible that acute pancreatic insufficiency also plays a part, with centrolobular necrosis preventing the transformation of carbohydrates into glycogen and their hepatic stockage.—H. Gounelle

Vitamin E deficiency has been repeatedly shown to produce degenerative myocardial changes in experimental animals. The loss of available reserve energy in the form of creatine phosphate may be related to these abnormalities. However, in the human, this vitamin has not been shown to have any effect upon the heart.

Phosphate and Glycogen Determinations in the Hearts of Vitamin E-Deficient Rabbits. A. G. Mulder, A. H. Gatz, and B. Tigerman. *Am. J. Physiol.* 179: 246, 1954.

Rabbit hearts were damaged by vitamin E deficiency. Examination of these tissues showed a reduction of creatine phosphate to 0.9 mg per cent from control values of 6.1 per cent. Glycogen, inorganic phosphate, and adenosine polyphosphate were unchanged. A rapid onset of dystrophy and weight loss was associated with the largest decreases in cardiac creatine phosphate.—M. J. Oppenheimer

Effect of Adrenalectomy on the Chemical Composition of Cardiac Muscle in Parabiotic and Single Rats. B. Hoelscher and D. D. Van Fossan. *Am. J. Physiol.* 179: 495, 1954.

Heart weights decreased and thymus weights increased in adrenalectomized parabiotic rats when these were compared to parabiotic intact animals. Such differences were not observed in adrenalectomized single rats. The hearts of adrenalectomized parabiotic rats were high in potassium and low in sodium, but such was not the case in adrenalectomized single animals. As a result of this difference in the potassium-sodium ratios between adrenalectomized single animals, the authors consider the possibility of a "parabiotic barrier" which prevents transfer of adrenal steroids through the anastomosis.—M. J. Oppenheimer

MIND AND METABOLISM

Mental development, as well as physical growth, is related to nutritional adequacy of the diet. Malnutrition in infants has been associated with delayed cerebration; nutritional deficiencies in adults are accompanied by striking mental aberrations. In addition to cerebral syndromes observed in patients of poor nutritional status, there are numerous examples of metabolic abnormalities in which the substrates derived from foods are not properly utilized, leading to mental symptoms. One of the rare innate metabolic errors associated with mental defects is phenylketonuria, which has been effectively treated by a unique modification of the diet.

Treatment of Phenylketonuria with a Diet Low in Phenylalanine. L. I. Woolf, R. Griffiths, and A. Moncrieff. *Brit. M. J.* 1: 57, 1955.

"Phenylketonuria is one of the very few conditions in which mental deficiency is associated with a demonstrable metabolic error. It has been suggested that the mental defect is due to an intoxication by phenylalanine or one of its metabolites, and that the mental deficiency may be relieved by feeding a diet low in phenylalanine."

Three subjects with phenylketonuria, two of them aged 2 years and 8 months and the other 5 years and

5 months, all with serious mental deficiency, have been treated by a carefully prepared diet low in phenylalanine for from 4½ to 10 months. Since all dietary proteins contain considerable quantities of phenylalanine, protein nitrogen was given as casein hydrolysate which had been freed of phenylalanine, tyrosine, and tryptophan by passing through charcoal; tyrosine and tryptophan were added separately.

The clinical features of these cases, together with biochemical investigation, the results of intelligence tests, and the diet, are presented in considerable detail and cannot be adequately summarized in an abstract.

Briefly, the rate of increase of mental age of all three children rose markedly while they were on the diet; their I.Q.'s rose, and it is considered that they may reach educable levels. One child ceased having attacks of petit mal and his electroencephalogram became normal soon after starting treatment; another child with petit mal developed status epilepticus on the diet but later improved. Growth and physical health were normally maintained.

The economics of this treatment is discussed. The dietary constituents cost, at the time of publication, 7 shillings and 4 pence (about one dollar) a day, in contrast to the cost of their eventual institutional stay at £5 ($14.20) per week.

"The most important point is that if costly treatment is to be justified it must be started early. *This means that the urine of every baby or young child in whom there is the slightest suspicion of mental retardation must be tested for phenylpyruvic acid.*"—F. E. HYTTEN

Mental efficiency has been shown to be increased by an adequate breakfast with sufficient protein to prevent the reactive hypoglycemia which occurs in mid-morning with high carbohydrate, low protein breakfasts. Similar benefits are derived from a mid-morning snack if the volume of food is not large.

Effect of Gastric Contents on Mental Concentration and Production Rate. R. C. Hutchinson. *J. Appl. Physiol.* 7: 143, 1954.

Mid-morning consumption of small amounts of solid food may increase ability to concentrate from the time food is consumed until lunch time. For those at work, this will almost certainly result in an increase in production rate. However, if the consumption of solid food exceeds 9–12 oz for sedentary occupations, there may be a decrease in production rate. The value of a full three-course meal consumed at any time during the working day is thereby limited.—M. J. OPPENHEIMER

The utilization of carbohydrate in patients with psychosis and other types of cerebral disorders have been reported sporadically as being abnormal. Some authorities have proposed that certain defects in carbohydrate metabolism observed in cerebral tissues are responsible for brain disease, such as psychoses. Further information is made available in the following studies, without establishing cause and effect relationships.

Carbohydrate Metabolism in Brain Disease. I. Glucose Metabolism in Multiple Sclerosis. D. H. Henneman, M. D. Altschule, R. M. Goncz, and L. Alexander. *Arch. Neurol. & Psychiat.* 72: 688, 1954.

Patients with multiple sclerosis show an abnormality in their carbohydrate metabolism. Fasting whole blood lactic and alpha-keto glutaric acid concentrations are elevated. After the oral administration of 100 g of glucose there is a lag in the return to fasting level of the true blood glucose; there is an excessive accumulation of lactic and, possibly, pyruvic acids, and a consistent rise, rather than the normal fall, in plasma citric acid and whole blood alpha-keto glutaric acid concentrations. These abnormalities suggest that there is a defect in the utilization of the small carbohydrate fragments in multiple sclerosis. This defect is not permanent, for the levels of glucose and of lactic, pyruvic, and citric acids return to the fasting values in time.—S. W. CONRAD

Carbohydrate Metabolism in Brain Disease. III. Fructose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses. D. H. Henneman, M. D. Altschule, and R. M. Goncz. *Arch. Neurol. & Psychiat.* 72: 696, 1954.

The authors administered pure fructose to a group of normal subjects and to patients suffering from schizophrenic, manic-depressive, and involutional psychoses. Fructose tolerance was the same for the normal and the psychotic groups. However, in the psychotic groups, there occurred a rise, rather than the normal fall, in true blood glucose concentration after fructose was given orally. (There was no significant difference in blood glucose when the fructose was administered intravenously.) The abnormal rise is due to the initial normal conversion of some fructose to glucose in the intestine and the subsequent sluggish utilization of this glucose. This rise, together with the entrance of some fructose into the metabolic pool, may explain the moderately increased accumulation of citric acid in the blood of the psychotic patients who received fructose. The finding of normal fructose tolerances in patients with the foregoing psychoses rules out any commonly recognized hepatic disease as the cause of reported disorders in intermediary carbohydrate metabolism.—S. W. CONRAD

Mongolism is a disease of unknown etiology which resembles cretinism in many of its clinical aspects. However, the thyroid function of these patients is

normal. It would be of interest to observe whether desiccated thyroid would reduce the elevated cholesterol and S_f 12–20 lipoprotein concentrations in patients with mongolism.

Metabolic Studies in Mongolism. (Serum Protein-Bound Iodine, Cholesterol, and Lipoprotein.) A. Simon, C. Ludwig, J. W. Gofman, and G. H. Crook. *Am. J. Psychiat.* 111: 139, 1954.

The authors studied the thyroid and lipid function in mongolism by comparing (1) the levels of serum protein-bound iodine, (2) cholesterol, and (3) the fraction of S_f 12–20 molecules of lipoproteins found in a group of mongoloid patients with the findings in a group of normals and a group of non-mongoloid mental defectives ("undifferentiated mental deficiency").

There were no significant differences in the serum protein-bound iodine levels of the mongoloids as compared to the "controls" of the same age. The serum cholesterol level of the mongoloid children is about the same as the level of the non-mongoloid mental deficiency group. However, both groups of mental defectives have significantly higher serum cholesterol levels than normal children. The most marked difference was in the level of large molecule lipoproteins of the S_f 12–20 class. The mongoloids had the highest elevations, the non-mongoloid mental defectives were intermediate, and the normals had the lowest level.

Elevated levels of S_f 12–20 molecules of lipoproteins are associated with increased tendency to atherosclerosis. Because mongoloids usually die early in life, the authors suspect that individuals with extensive disturbance in lipoprotein metabolism tend to die even before structural atherosclerotic changes are evident.—S. W. Conrad

NUTRITION IN INFANCY

Breast feeding is regarded generally as the most desirable program for maintaining infant nutrition. However, there may be circumstances which render this type of feeding impractical. The following analysis of the caloric values of artificial feedings for infants discloses several interesting facts. The caloric requirements for the majority of infants fell short of minimum standards. In a report by Albanese (this Journal *3: 121, 1955), lysine supplementation of milk improved its nutritive value, leading to an increase in body weight. In the following report, weight gain was more rapid in those infants receiving high caloric intakes, without reference to the lysine level of the diet.*

Artificial Feeding and Energy Requirements of Young Infants. F. E. Hytten and I. A. G. McQueen. *Lancet* 2: 836, 1954.

Government-subsidized "National dried milk" for infants is provided in Britain in half-cream and full-cream varieties. Reconstituted mixtures were prepared in the laboratory following instructions printed on the containers. Full-cream milk, in the quantities recommended, provided barely sufficient calories to meet the theoretical calorie requirements of infants, and half-cream feeds appeared to be seriously deficient in energy. The requirement standard used for comparisons is 55 calories per pound (120 calories per kilogram) body weight daily.

One hundred samples of milk mixtures routinely prepared by mothers in their homes for infants under three months of age were collected by Health visitors, who also noted the total quantity fed, the general health and weight gains of the babies, and the general competence of the mothers. "Expected" weights of infants were calculated from the formula: birth weight + 1 oz per day of life, neglecting the first ten days. Seventy-three of the milk samples had been prepared from National dried milk (34 full-cream, 27 half-cream, and 12 from a mixture), 23 from cow's whole milk, and 4 from proprietary dried milks. Most mixtures contained added carbohydrate. Calculating from the composition of the mixtures, the reported quantities fed, and the expected weights of the babies, it was found that 69 of the 100 infants were receiving less than 120 calories per kilogram per day, and 49 less than 100 calories. The overall range was from 50 to 220 calories per kilogram daily. Feeds prepared by the more competent mothers showed a narrower range of composition than those prepared by the less competent, but in all groups there seemed to be a considerable amount of underfeeding. Babies with higher calorie intakes were gaining weight more rapidly and seemed to be healthier than those on low calorie intakes. There was no evidence that babies on mixtures with the highest calorie contents suffered from any digestive disturbances. Revision of the instructions on tins of National dried milk is recommended.—F. E. Hytten

The Metabolic Influence of Changes in the Ratio of Fat to Carbohydrate in Infant Nutrition. J. T. Lanman, E. L. Pratt, P. M. Norton, S. Morales, S. E. Snyderman, and L. E. Holt, Jr. *Am. J. Dis. Child.* 88: 809, 1954.

By conducting balance studies, the authors have evaluated the effect of substituting fat for carbohydrate in the diet. It was confirmed that isocaloric substitution of carbohydrate for fat results in a temporary spurt in weight, followed by resumption of the normal curve. When fat is returned to the diet there is a temporary weight loss during the subsequent three or four days, with a resumption of the normal curve. Balance studies of sodium, chlorine, potassium, and nitrogen, and measurement of body water indicate that the intracellular compartment participated in the weight gain during high carbo-

hydrate intake, and the free amino acid excretion increased while the nitrogen excretion decreased and vice versa.—J. N. Etteldorf

The addition of lactose to cow's milk in artificial infant feeds has been practiced for many years. This sugar, when split, gives rise to glucose and galactose and is less sweet than sucrose.

Lactose in Infant Feeding. P. Delthil. *Sem. Hôp. Paris* 45: 2335, 1953.

The author shows the advantages of lactose, its effects on the intestinal flora, on the assimilation of minerals, and on the myelinization of the nerve fibers.

He selects certain essential indications, particularly saccharose dyspepsia, to which lactose serves as an antidote.

The addition of 3 per cent lactose to cow's milk permits the re-establishment of a balance approaching the carbohydrate balance of the mother's milk during the first semester.—H. Gounelle

Saccharose Intolerance in the Infant. P. Delthil. *Presse méd.* 61: 1643, 1953.

Saccharose intolerance is relatively common. It is manifested in the infant in the first trimester by various cutaneous or digestive disorders which are in contrast to the good general condition of the child and a normal weight curve.

In the infant, saccharose dyspepsia is usually the result of an excessive intake of sweets; the resulting clinical pictures are various, the most common being *prurigo strophulus*.—H. Gounelle

In animal nutrition, deficiency of certain unsaturated fatty acids will produce skin lesions and other signs of disease. The administration of linoleic or arachidonic acids will reverse these disorders. It has been suggested that infants may develop eczema in association with low serum content of these "essential fatty acids." However, the final decision concerning the human requirements of these factors awaits more conclusive study.

Essential Fatty Acids and Human Nutrition. I. Serum Level for Unsaturated Fatty Acids in Healthy Children. H. F. Wiese, R. H. Gibbs, and A. E. Hansen. *J. Nutrition* 52: 355, 1954.

On the basis of reports published on dogs, it appeared feasible to use the serum level of linoleic and arachidonic acids as a means of evaluating the nutritional significance of these fatty acids in children. First, however, it was necessary to establish the serum level of unsaturated fatty acids in healthy children, particularly in relation to the dietary intake of specific fatty acids. The results of such a study are summarized in this paper.

The blood serum levels for dienoic, tetraenoic, and hexaenoic acids were determined on 93 well-nourished infants and children. The serum levels for 2, 3, and 4 double-bond fatty acids were found to be in the same range for both well-nourished hospitalized children and healthy non-hospitalized children. There appears to be a slightly lower level for dienoic and tetraenoic acids in the serum of infants than in the children 2 to 15 years of age. The trienoic acid content of the serum for healthy children is relatively low.

On a dietary intake comprising 3 per cent of the total calories as linoleic acid, the mean serum level of 2, 3, and 4 double-bond fatty acids for 60 healthy control children 4 to 15 years of age were, respectively, 30.3, 1.5, and 10.2 per cent of the total fatty acids. On the basis of these blood levels, the data indicate that there is no dietary requirement for arachidonic acid for healthy children when linoleic acid is supplied. The hexaenoic acid content of the serum of healthy children shows wide variations. The significance of pentaenoic and hexaenoic acids in the serum of healthy children is not known.—B. Sure

Essential Fatty Acids and Human Nutrition. II. Serum Level of Unsaturated Fatty Acids in Poorly-Nourished Infants and Children. A. E. Hansen and H. F. Wiese. *J. Nutrition* 52: 367, 1954.

The blood serum levels for the total fatty acids, dienoic, trienoic, tetraenoic, and hexaenoic acids, were determined on 57 poorly nourished infants and children. There were no significant differences in the amount of the total fatty acids in serum of children in fair and poor nutritional states as compared with well-nourished children. Dienoic, tetraenoic, and hexaenoic acid levels in the serum of inadequately nourished children were significantly lower than in healthy children. The trienoic acid level in the serum of inadequately nourished children was significantly higher than in healthy children.—B. Sure

The following report is reminiscent of a recently introduced method of evaluation of pancreatic function utilizing radioiodine-labeled albumin. When such techniques are employed, the patient must be prepared with Lugol's solution to saturate the thyroidal iodine space, thus preventing the uptake of I^{131} by the gland.

Use of I^{131}-Labeled Corn Oil to Measure Digestion and Absorption of Fats in Infants and Children. Y. Van Erp, F. J. Lemm, and S. Spector. *Am. J. Dis. Child.* 88: 800, 1954.

It was observed, in an unstated number of infants, utilizing I^{131}-labeled corn oil, that 20 per cent of administered fat was excreted in the stool prior to one year of age and 3 per cent appeared in the stools in individuals over one year. In cases of cystic fibrosis

of the pancreas, 37 per cent of the oil appeared in the feces in cases under one year of age and 49 per cent over one year of age.

This apparently is a preliminary report, and one is curious concerning the dosage of I^{131} and the uptake by the thyroid gland.

The findings are in line with expectations and illustrate the progressive nature of fibrocystic disease of the pancreas.

Silverman and Shirkey have recently re-introduced the use of iodized oil as a means of studying fat absorption and recommend its use as a screening test in the diagnosis of fibrocystic disease of the pancreas. Urinary iodine excretion is used as an index of absorption.—J. N. Etteldorf

Sodium retention appears to be an important feature in infantile nutritional edema, as in the edema associated with protein malnutrition in adults. The negative balance for sodium associated with loss of edema due to malnutrition has been demonstrated in all age groups. Potassium deficiency may represent one of the consequences of malnutrition, rather than a factor responsible for edema formation.

Potassium Deficiency in the Pathogenesis of Nutritional Oedema in Infants. J. D. L. Hansen and J. F. Brock. *Lancet* 2: 477, 1954.

Sodium, potassium, chloride, and nitrogen balance studies were carried out on six infants with nutritional edema; all had hypoalbuminemia and some conformed to the description of kwashiorkor. From the onset of treatment with skimmed milk formulae there was a very considerable retention of potassium and nitrogen. There was a small initial retention of sodium and chloride for 2 or 3 days, followed by a large negative balance accompanied by loss of edema. In two cases, treatment with a mixture of sodium and potassium salts, glucose and water was used for 4 or 5 days before introducing the milk mixture. In both of these potassium was retained and there was a negative balance of sodium, chloride, and water; there was no change in serum protein levels during the period. It is suggested that electrolyte imbalance is important in the pathogenesis of nutritional edema of this type.—F. E. Hytten

Vitamin D, rather than the calcium:phosphorus ratio, appears to be the most important factor in the maintenance of serum calcium levels in infants.

The Effects of Diets Varying in Ca:P Ratio and Total Calcium and Phosphorus on Serum Calcium Levels in Infants During the First Week of Life. J. B. Pincus and I. F. Gittleman. *Am. J. Dis. Child.* 88: 803, 1955.

Large numbers of infants were fed formulae with variable Ca:P ratio, with the following results:

Group	No. infants	Ca:P	Serum Ca less than 8 mg% on 5th day
1*	75	1.5:1	17
2*	60	2.1:1	35
3†	29	2.6:1	3
4†	63	1.9:1	6.3
5†	38	3:1	2.5

* No vitamin D with whole milk formula.

† Received vitamin D with formula basis of casein.

The serum Ca fell below 8 mg per cent in a greater percentage of groups 1 and 2 receiving no vitamin with whole milk formula. This fall was not dependent upon the Ca:P ratio of the diet. The calcium level of the serum remained above 8 mg per cent at the fifth day of age in a considerably greater number of infants who received vitamin D and a formula the basis of which was casein. In this group, an increase in the Ca:P ratio in the formula was reflected in an increase in the serum calcium level.

It is difficult to interpret accurately the results as given in the author's abstract, since neither the fat nor vitamin D content was similar in the two groups. —J. N. Etteldorf

NUTRITION IN THE OLDER CHILD

The feeding programs planned for children should provide meals designed to supply the nutrients required for growth and health, and should aid the child in learning the proper selection of foods when left to his own resources. There are many psychologic and physical factors which have to be recognized in such feeding programs. These are discussed in the Dietotherapy section of this Journal *3: 150, 1955, and in the following excellent reports.*

Appetites and Attitudes, A Viewpoint on Feeding the Young Child. M. G. Wagner. *J. Am. Dietet. A.* 30: 329, 1954.

This is an interesting discussion of the feeding practices in the nursery school at Merrill Palmer School. Application is made to home and hospital situations. The basic principle underlying feeding at the school is to introduce as wide a variety of foods as possible in a relaxed, casual atmosphere. The procedure is oriented around what seem to be focal points of adult-child interaction in the feeding situation at home and at school. These are (a) limited self-selection of diet; (b) self-help; (c) elimination of moral values usually attributed to acceptance or rejection of certain foods; and (d) introduction of new foods.

The entire meal, including dessert, is placed on the table in small uncovered casserole dishes. Each child takes as *little* or as much of the food as he wishes with no comment from the teacher as to acceptance or rejection. No comments are made which imply that "food is good, but not good for you" or that it "is not good but good for you." The adult

controls the situation in that he controls the kind of food presented. The meal is essentially high protein, low carbohydrate, and desserts are preparations of egg, milk, or fruit.

Learning new foods is managed by including variety, acquainting the children with the new food before it is prepared, and introducing it with familiar, well-liked foods. No restriction is made on children as to the manner or method of eating. Manners are taught by example and the use of fork or spoon is no longer stressed. Since children are very conscious of the "feel" of foods, opportunities are given to experiment with finger foods—pieces of raw foods in sizes easily manipulated. Bread and butter made into sandwiches are cut into quarters. Children really prefer simple unmixed food.

Some points emphasized in helping families with food problems are: (1) self-selection at the family dinner table can mean simply allowing the child to choose between two or three raw vegetables; (2) appetites can be encouraged if small portions are served; (3) interest in food and eating can be encouraged by allowing the child to assist in simple preparations and participate in menu planning; (4) self-service offers a chance to develop fine motor skills and is no problem if foods are easy to serve; (5) foods should be simply prepared and unmixed; (6) desserts should be removed from the reward class and can be if made of egg and milk or fruit; (7) "finger foods" provide opportunity for the child to associate color and texture with the flavor of food; (8) the tools of eating and the food should be suited to the developmental level of the child. Similar points apply to the hospital. The parent can serve as the link between home and hospital care.

It would have been interesting to see some data on the extent of acceptance of food among children fed according to earlier and present practices at Merrill Palmer School.—J. M. Smith

A Bookshelf on Nutrition and the Preschool Child. L. Weng. *J. Am. Dietet. A.* 30: 570, 1954.

This is a review of sources of information on the subject of nutritional needs of the preschool child. It presents publications grouped according to the following areas: (a) food requirements and meal planning; (b) guiding the children in learning to eat; (c) meals away from home; and (d) suggestions for parents. Each section lists information sources from books, pamphlets, and original research articles, with a comment on the particular contribution of each source.

A bibliography of 45 references supplies a valuable reading list. According to the reviewer's experience, the sources are authoritative and well-written. This information will be of value to teachers, pediatricians, nutritionists, parents, and persons "reading just for the fun of it."—J. M. Smith

The effect of the omission of breakfast or of a high carbohydrate feeding at breakfast has been frequently investigated. The results have consistently demonstrated a decrease in efficiency in various age groups, including those of school age investigated in the following report, when a properly balanced breakfast is not consumed.

Effect on School Boys of Omitting Breakfast, Physiologic Responses, Attitudes and Scholastic Attainments. W. W. Tuttle, K. Daum, R. Larsen, J. Salzano, and L. Roloff. *J. Am. Dietet. A.* 30: 674, 1954.

This investigation was designed to test the effects of the omission of breakfasts on physiologic responses, mental attitudes, and scholastic attainments of boys 12–14 years of age.

The study is comprised of "controlled diet" and "unrestricted diet" experiments. In the former, diets were prepared and served at the University Hospital cafeteria. Seven boys completed the study, which was conducted during the school year, and laboratory observations were supplemented by those of the school principal and teachers. The latter study, conducted during the summer, covered 18 boys who ate at their several homes and came to the laboratory for tests. No school observations were included.

The data presented in this paper are those of the controlled diet group. The experimental plan for this group was as follows: (1) Preliminary period—3 weeks; during this time the diet pattern of the boys was studied and training was given in physiologic tests. (2) Experimental period—14 weeks; divided into five parts as follows: basic cereal-and-milk breakfast—4 weeks; no breakfast—2 weeks; basic cereal-and-milk breakfast—3 weeks; no breakfast—2 weeks; basic cereal-and-milk breakfast—3 weeks.

In the basic period, meals were served at 7:30 a.m., 11:30 a.m., and 5:00 p.m., with an evening lunch served before 8:00 p.m. During the "no breakfast" period, food was not served between 8:00 p.m. and 12:00 noon the following day. Nutrient intakes were the same during the "basic" and "no breakfast" periods, though distribution throughout the day differed.

The following physiologic responses were measured: (a) Neuromuscular tremor magnitude. (b) Choice reaction time. (c) Maximum grip strength. (d) Grip strength endurance. (e) Maximum work rate. (f) Maximum work output. Tests were made at comparable intervals during each of the five experimental periods according to techniques previously reported. Mean responses to the six tests are shown for each of the seven subjects during the basic and no breakfast periods. Differences were tested for significance by the "t" test. The data for the eighteen boys on the unrestricted diets were compared by group means only and verified the findings of the controlled diet group.

As a result of these studies the authors conclude: "Neuromuscular tremor magnitude, choice reaction time, grip strength, and grip strength endurance were unaffected by the omission of breakfast.

"Maximum work rate and maximum work output were significantly less in the late morning hours during the period when breakfast was omitted.

"It was the consensus of the school authorities that the omission of breakfast exerted a significant, detrimental effect both on the attitudes and scholastic attainments of the boys."—J. M. SMITH

The absorption of calcium from the intestinal tract is decreased by the formation of insoluble complexes with phytates and oxalates within the intestinal lumen. In young subjects with high calcium requirements, it is comforting to observe that the phytate from foods removed significantly less calcium than does the free phytate.

Studies in Calcium Metabolism. Effect of Food Phytates on Calcium[45] Uptake in Children on Low-Calcium Breakfasts. F. Bronner, R. S. Harris, C. J. Maletskos, and C. E. Benda. *J. Nutrition* **54**: 523, 1954.

Nineteen adolescent boys, of inadequate intelligence, but otherwise normal, who were institutionalized under uniform nutritional and other environmental conditions, were given three types of breakfast low in calcium: (1) oatmeal, (2) farina, and (3) farina and sodium phytate. These meals contained, respectively: 55, 60, and 60 ml of milk; 91, 83, and 83 mg of calcium; 116, 0, and 78 mg of phytic phosphorus, and 0.85, 0.85, and 0.85 μc of radioactive calcium (Ca^{45}). Calcium uptake was studied by measuring the Ca^{45} content of serum, urine, and feces for a period of 5 days. Individual variations were controlled by placing each subject on two different Ca^{45}-labeled breakfasts, 30 days apart.

The uptake of Ca^{45} by the boys on the oatmeal breakfast was 74 per cent as great as that of the boys on the farina breakfast. Similarly, the uptake of Ca^{45} by the boys on the farina plus phytate meal was 45 per cent that of farina meal. These differences proved to be statistically significant on a 5 per cent probability level.

Significantly less Ca^{45} was taken up in the presence of sodium phytate than in the presence of an equivalent quantity of phytic phosphorus supplied by oats. —B. SURE

SCURVY, ASCORBIC ACID, AND STRESS

The recognition of scurvy is not a simple problem in modern medicine. The diagnosis of this condition is frequently based upon the evidence of cutaneous or gingival bleeding and upon the presence of anemia, together with a nutritional history indicating an inadequate consumption of foods providing vitamin C. The laboratory aids useful in supporting the diagnosis of scurvy are not generally available, so that a therapeutic response to ascorbic acid is of paramount value.

Scurvy—A Rare Disease? T. J. Thomson. *Glasgow M. J.* **35**: 363, 1954.

Scurvy is widely held to be a rarity in Britain among adults. In the past 15 years, Stobhill General Hospital, Glasgow, has admitted 100 cases of "florid scurvy." The annual incidence was between 4 and 7 cases, with peaks of 14, 10, and 9 in 1942, 1944, and 1953. The maximum incidence is during the summer, there being a sudden increase in May and a maximum in June. "No doubt this is attributable to depletion of tissue reserves built up in the preceding summer."

There were only six women in the series, and most cases were men in their seventh and eighth decades who lived alone and did their own cooking.

The most striking clinical sign was widespread subcutaneous hemorrhages of the lower limbs; there was a high percentage with marked anemia. Many cases were undiagnosed before admission.

"Recovery was complete in 95 cases. The five deaths were attributed to myocardial infarction (2), pneumonia, haemorrhage from a chronic duodenal ulcer, and inanition."

It is suggested that a good deal of vague ill health attributed to "old age" may be due to subclinical scurvy.—F. E. HYTTEN

A Case of Scurvy Simulating a Gastric Neoplasm. K. Dewhurst. *Brit. M. J.* **2**: 1148, 1954.

This detailed case report describes an epileptic man of 72 living alone on a diet of milk, bread, and soup, who presented with (among numerous other symptoms) increasing anorexia, epigastric pain unrelated to meals, fatigue, and a loss of 28 pounds weight. He had had a hematemesis and was in poor condition on admission to hospital. He was thought to have an anterior cardiac infarction and scurvy, but a radiological examination of the stomach showed a prepyloric ulcer suggestive of carcinoma. The man's condition improved very rapidly with appropriate diet and one month after the first examination, a second x-ray showed a normal stomach; this was confirmed by biopsy. It is suggested that the lesion simulating carcinoma was a submucous hematoma.—F. E. HYTTEN

Scurvy in Old Age. W. Hughes and D. C. MacLennan. *Brit. M. J.* **2**: 1149, 1954.

Gross nutritional deficiency, largely presenting as scurvy, is described in a widower of 80 who lived alone. He had sufficient means for comfortable living, but was mentally incapable of caring for himself.

Whereas widows tend to preserve the home and care for themselves after their partners die, widowers on the whole do not. Meal services are available through the local authority, but they fail in such a case as this, where no advantage is taken of them because of feeble mentality.—F. E. HYTTEN

Variability in the Measure of Total Ascorbic Acid and Utilization by the Human. K. H. Fisher and M. L. Dodds. *J. Nutrition* 54: 389, 1954.

The two factors of variability studied have been an outgrowth of an investigation of total ascorbic acid utilization by the human. The factors are the carry-over effect of previous intake of total ascorbic acid on subsequent data and the effect of the same amount of a test dose of ascorbic acid given either at a single time or divided by an interval of time. In addition, the sensitivity of blood plasma and urine measurements as a means of differentiating changes in ascorbic acid intake has been studied. Total ascorbic acid measurements of the blood plasma and of 24-hour urine returns were the measures.

From the data obtained under the conditions of these experiments it is concluded that:

(1) The carry-over effect of both high and low intakes of total ascorbic acid is still evident in the blood plasma for at least 23 days after transfer to a new intake level. The excretion of total ascorbic acid appears to adjust more quickly than does the blood plasma level.

(2) There are no significant differences in blood plasma or urinary total ascorbic acid values when the same amount of the vitamin, either 75 or 150 mg, is ingested as a single or divided intake.

(3) Blood plasma levels and 24-hour urine returns of total ascorbic acid are demonstrated to differentiate between intakes of 60 and 75 mg for 8 subjects at each level (significant 1 per cent level). Differentiation is suggested by as few as three subjects at each level (significant 5 per cent level).—B. SURE

The stressful circumstances associated with pregnancy increase the nutritional demands of the individual for protein and essential accessory food factors. The reduction noted in the incidence of decidual hemorrhage and abortion following vitamin C administration is further evidence supporting the need for dietary supplementation during pregnancy.

Pathology of Spontaneous Abortion. II. Relationship of Decidual Hemorrhage to Spontaneous Abortion and Vitamin C Deficiency. C. T. Javert. *Texas State J. M.* 50: 652, 1954.

Decidual hemorrhage was found in 61 per cent of spontaneous abortion specimens in a group of 1334 patients.

Plasma vitamin C concentration decreased in normal pregnancy from an average value of 1 mg to 0.29 mg per 100 ml at term. About 45 per cent of the total group of normal pregnant, threatened, and spontaneous abortion cases had blood levels under 0.5 mg per 100 ml. Less than one-third of non-pregnant women had such low levels.

Maternal vitamin C deficiency was found in 57 per cent of cases of spontaneous abortion with decidual hemorrhage, and in only 31 per cent without decidual hemorrhage.

Postpartum and antepartum therapy with vitamins C and K in 100 patients with histories of habitual abortion yielded a successful outcome in 91 per cent. —S. O. WAIFE

The significance of ascorbic acid in surgical patients has been well established. It is customary to flood these patients with this vitamin during parenteral fluid therapy incident to surgery by adding 0.5 to 1.0 g of vitamin C to intravenously administered fluids daily, together with vitamin B complex.

Ascorbic Acid Deficiency in Surgical Patients. J. H. Crandon, S. Mikal, and B. R. Landeau. *Proc. Brit. Nutrition Soc.* 12: 273, 1953.

From analyses of blood tissues in surgical patients it appears that blood ascorbic acid levels are of value in estimating deficiency of this vitamin. In the surgical patient, blood ascorbic acid below 0.2 mg/100 ml is suggestive of serious ascorbic acid deficiency. Nevertheless, with plasma ascorbic acid below this level, wound healing has been observed to occur, provided the buffy-coat ascorbic acid remained above 8 mg/100 g, and provided there was no wound infection or other increased local stress. The plasma determination is considered to be of more value than the buffy-coat determination in assessing ascorbic acid nutrition in surgical patients.

Scurvy, in many cases, appears to be a manifestation not of complete absence of ascorbic acid alone, but of marked ascorbic acid deficiency plus local tissue stress. Surgical patients having a deficient plasma and buffy-coat ascorbic acid are frequently very ill, have a relatively poor prognosis, and have a high incidence of evisceration, incisional hernias, and draining wound sinuses postoperatively.—B. SURE

In the chronic diseases appearing in aging patients, similar benefits may be derived from the use of vitamin C as in the case of surgical patients. However, the manifold factors involved in the evaluation of results obtained with its use make it mandatory that a controlled study be employed.

Chronic Disease and Vitamin C. L. C. Cass, W. S. Frederik, and J. D. Cohen. *Geriatrics* 9: 375, 1954.

In this study 140 persons were observed bi-weekly for five months at the Long Island Hospital in Boston. About half the group were "ambulatory";

the others included 39 arthritics, 25 diabetics, and 12 patients with disabling multiple sclerosis. All were "elderly," though neither specific nor average ages are stated.

It was observed that: (1) institutionalized elderly persons receive very little fresh fruit in their diet and have low whole blood vitamin C levels, averaging 0.35 mg per cent; (2) eight ounces orange juice daily raised the ascorbic acid level to an average of 1.52 mg per cent; (3) average sedimentation rates were elevated; (4) the blood cholesterol values in these elderly patients with chronic diseases were within normal limits; (5) arthritic patients receiving a high ascorbic acid intake reported less pain, some improvement in sense of well-being and appetite, but no notable improvement in the athritic lesions (similar subjective improvement was noted by the patients suffering from multiple sclerosis); (7) four grams ascorbic acid daily for as long as three months caused no apparent toxic effects.—E. J. Stieglitz

Use of Vitamin C in Acne Vulgaris. G. E. Morris. *A.M.A. Arch. Derm. & Syph.* 70: 363, 1954.

There are several reasons why vitamin C "should" be tried in acne vulgaris. This vitamin plays a role in normal keratinization, lack of it producing hyperkeratosis. Furthermore, there was an exacerbation of acne in volunteers deprived of vitamin C.

The author of this brief paper gave 53 patients an 8-oz glass of citrus juice twice daily, as well as ascorbic acid (3 g/day). Of these patients, most of whom were followed for an average of four months, 43 improved. These included 15 who had been treated for months or years by all usual methods without success. Ten patients failed to improve, and 7 did not return for an adequate follow-up. It should be mentioned that, in addition to the large doses of vitamin C, all patients were also given a "diet free of chocolate, cocoa, nuts, and peanut butter, were told to clean their skin three times a day, and were given sulfurated potash (lotio alba) to apply at night." From his experience the author concludes that vitamin C seems to play an important part in certain cases of acne.—S. O. Waife

Because of the importance of the acclimatization to cold in military forces operating at low environmental temperatures, studies such as the following will continue to be actively pursued. The relationship between ascorbic acid and the function of the pituitary-adrenal axis, which plays an important role in stress tolerance, stimulates research upon the ability of the vitamin to facilitate or improve acclimatization.

Studies on Acclimatization and on the Effect of Ascorbic Acid in Men Exposed to Cold. J. LeBlanc, M. Stewart, G. Marier, and M. G. Whillans. *Canad. J. Biochem. & Physiol.* 32: 407, 1954.

Two main experiments were performed. In one, 12 men were confined to a room for 13 days, first for two days at 79 ± 1° F on normal rations, and then for 11 days at 59 ± 1° C on a "survival" ration of carbohydrate which supplied about 550 calories daily. The men wore only shorts, socks, and low shoes during the day, and were covered by one sheet and one blanket at night. Six of them were given 525 mg of ascorbic acid daily (giving a mean blood concentration of 1.6 mg per 100 ml) and the other six were given similar pills containing only 25 mg of ascorbic acid (giving a mean blood concentration of 0.8 mg per 100 ml). Water intake was unrestricted.

In the following changes which were observed with exposure to colder environment, no difference was seen between high and low ascorbic acid groups:

(1) A rapid drop in body weight.

(2) A drop in nitrogen excretion.

(3) An increased excretion of ketone-bodies.

(4) An initial fall in daily water intake to about 400 ml, followed by a gradual rise to about 6–700 ml.

(5) An immediate rise in water output ("cold diuresis") followed by a steep fall.

(6) A fall in chloride excretion.

(7) An initial rise in both red and white blood cell counts, followed by a gradual return to normal.

(8) A diminution in the excretion of 17-ketosteroids.

In the following there were significant differences between the high and low ascorbic acid groups:

(1) The B.M.R., taken at rest in bed, fell to about —20 per cent in the high vitamin C group only.

(2) Daytime skin temperatures, which fell at the beginning of the experimental period and then rose slowly, rose more quickly, and were in general higher in the high vitamin C group in those places on the body with a good layer of subcutaneous fat.

(3) The eosinophil count, which showed an increase in the morning and a fall in the afternoon was always higher in the high vitamin C group.

(4) Following the experiment all subjects experienced some "foot trouble" varying from mild paresthesia for one day to severe pain with difficulty in walking for 15 days. The high vitamin C group had very much less trouble than the rest both in intensity and duration.

(5) The sensation of discomfort due to cold was less in the high vitamin C group.

In a brief discussion it is considered that the higher skin temperature and the lower incidence of "foot trouble" may be due to an enhanced peripheral circulation in the subjects having a high intake of vitamin C on this type of ration.

In the second, similar experiment, two groups of three men were used as subjects, but they were fed on the Canadian Five-Man Ration Pack supplying an average of 3400 calories daily. Due to technical difficulties with environmental temperature regulation, the two experiments are not directly comparable from this point of view.

In this experiment there was no acclimatization to cold noted, except for an indication that the adrenal cortex may have been responding to stress, indicated by an initial increase in the excretion of 17-ketosteroids, followed by a fall and then a return to normal values. There were no differences between the high and low vitamin C groups.—F. E. HYTTEN

Adrenal, Pituitary and Urinary Ascorbic Acid Levels in Rats Subjected to Hypothermic Environment. S. Katsh, G. F. Katsh, and P. Osher. *Am. J. Physiol.* 178: 457, 1954.

Male albino rats were kept at 2°–4° C environmental temperatures. They were sacrificed at intervals up to 28 days. At the time at which they were sacrificed the adrenal and pituitary glands were weighed. These were then analyzed for ascorbic acid. After one day in the cold, adrenal weight and vitamin C contents were increased over the values in control rats. At this same period, pituitary vitamin C was reduced, although by the 28th day it was greatly increased. The increased ascorbic acid levels in the hypertrophied adrenals coincide with the higher plateau of interaction between hypophysis and adrenal cortex at the time of stress. The authors express the opinion that the pituitary-adrenal axis which is in readiness to maintain animals in a steady state is able to cope with increased demands when they are placed upon it. Urinary ascorbic acid was the same in controls and in cold-stressed rats. This may be an expression of a mechanism for conserving the vitamin.—M. J. OPPENHEIMER

The role of the adrenal ascorbic acid content in sterolgenesis is not clear. It has been suggested that the vitamin is necessary for the formation of the steroid hormones within the adrenal cortex. However, this concept does not receive support in the following study.

The Relation of Adrenocortical Function to Scurvy in Guinea Pigs. The Effect of Exogenous ACTH and Adrenalectomy. B. E. Clayton and F. T. G. Prunty. *J. Endocrinology* 9: 370, 1953.

Guinea pigs maintained on scorbutic diets showed a profound fall in adrenal gland ascorbic acid levels. This fall was striking by the twelfth day of the diet, and by the time the animals were moribund (after 21 days) essentially no ascorbic acid was present in the gland. Twenty mg ACTH was administered as 8 subcutaneous injections of 0.5 ml at hourly intervals on the 19–23 days of the diet. The urinary 17-ketosteroid output was determined and found to vary from 40–206 per cent of the saline-treated controls. The survival time of these ACTH-treated animals was uninfluenced, though hemorrhagic manifestations were somewhat accentuated.

Adrenalectomized guinea pigs, maintained on DCA and salt, when placed on scorbutic diets, in contrast to normal animals, died rapidly (within 3, 5, and 7 days), though hemorrhagic manifestations and bone changes were less striking. No ketosteroid rises were seen, though control (non-adrenalectomized) animals on DCA, salt, and scorbutic diets showed greater 17-ketosteroid rises than control scorbutic animals without DCA.

These experiments indicate that though the adrenal gland contains relatively large amounts of ascorbic acid, this ascorbate is not essential for adequate adrenal cortical function as manifested by responsiveness to ACTH. This adrenal ascorbate appears to act as a reservoir, probably accounting for the longer survival of normal animals as contrasted with adrenalectomized animals on a scorbutic regimen.—L. RECANT

Effects of Cortisone, Ascorbic Acid and Piromen on Phagocytosis in Mice. S. Marcus, D. W. Esplin, and G. A. Hill. *Proc. Soc. Exper. Biol. & Med.* 84: 565, 1953.

Under appropriate experimental conditions, the administration of cortisone and of Piromen intensified the phagocytic activity in the spleen, as measured by Thorium dioxide uptake. It also augmented peritoneal phagocytosis. Ascorbic acid augmented the latter, but did not affect splenic phagocytosis. No particular effect of any of these agents against Klebsiella pneumoniae was demonstrable.—L. W. KINSELL